

86/02/07  
JC540 U.S. PTO  
Practitioner's Docket No. 47578

PATENT

JC540 U.S. PTO  
09/176067  
10/20/98

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Patent Application  
Assistant Commissioner for Patents  
Washington, D.C. 20231

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of

**Inventor(s): Graham J. DURANT and Seetharamaiyer PADMANABHAN**

**WARNING:** 37 CFR 1.41(a)(1) points out:

"(a) A patent is applied for in the name or names of the actual inventor or inventors.

(1) The inventorship of a nonprovisional application is that inventorship set forth in the oath or declaration as prescribed by § 1.63, except as provided for in § 1.53(d)(4) and § 1.63(d). If an oath or declaration as prescribed by § 1.63 is not filed during the pendency of a nonprovisional application, the inventorship is that inventorship set forth in the application papers filed pursuant to § 1.53(b), unless a petition under this paragraph accompanied by the fee set forth in § 1.17(i) is filed supplying or changing the name or names of the inventor or inventors."

**For (title): PHARMACEUTICALLY ACTIVE COMPOUNDS AND METHODS OF USE**

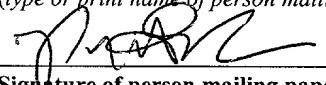
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CERTIFICATION UNDER 37 C.F.R. 1.10\*

(Express Mail label number is **mandatory**)  
(Express Mail certification is optional.)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on this date October 20, 1998, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number EL014417763US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Peter F. Corless  
(type or print name of person mailing paper)

  
Signature of person mailing paper

**WARNING:** Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.

**\*WARNING:** Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).

"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.

## 1. Type of Application

This new application is for a(n)

(check one applicable item below)

- Original (nonprovisional)
- Design
- Plant

**WARNING:** *Do not use this transmittal for a completion in the U.S. of an International Application under 35 U.S.C. 371(c)(4), unless the International Application is being filed as a divisional, continuation or continuation-in-part application.*

**WARNING:** *Do not use this transmittal for the filing of a provisional application.*

**NOTE:** *If one of the following 3 items apply, then complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF A PRIOR U.S. APPLICATION CLAIMED and a NOTIFICATION IN PARENT APPLICATION OF THE FILING OF THIS CONTINUATION APPLICATION.*

- Divisional.
- Continuation.
- Continuation-in-part (C-I-P).

## 2. Benefit of Prior U.S. Application(s) (35 U.S.C. 119(e), 120, or 121)

**NOTE:** *A nonprovisional application may claim an invention disclosed in one or more prior filed copending nonprovisional applications or copending international applications designating the United States of America. In order for a nonprovisional application to claim the benefit of a prior filed copending nonprovisional application or copending international application designating the United States of America, each prior application must name as an inventor at least one inventor named in the later filed nonprovisional application and disclose the named inventor's invention claimed in at least one claim of the later filed nonprovisional application in the manner provided by the first paragraph of 35 U.S.C. 112. Each prior application must also be:*

- (i) An international application entitled to a filing date in accordance with PCT Article 11 and designating the United States of America; or*
- (ii) Complete as set forth in § 1.51(b); or*
- (iii) Entitled to a filing date as set forth in § 1.53(b) or § 1.53(d) and include the basic filing fee set forth in § 1.16; or*
- (iv) Entitled to a filing date as set forth in § 1.53(b) and have paid therein the processing and retention fee set forth in § 1.21(l) within the time period set forth in § 1.53(f).*

*37 CFR 1.78(a)(1).*

**NOTE** *If the new application being transmitted is a divisional, continuation or a continuation-in-part of a parent case, or where the parent case is an International Application which designated the U.S., or benefit of a prior provisional*

*application is claimed, then check the following item and complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.*

**WARNING:** *If an application claims the benefit of the filing date of an earlier filed application under 35 U.S.C. 120, 121 or 365(c), the 20-year term of that application will be based upon the filing date of the earliest U.S. application that the application makes reference to under 35 U.S.C. 120, 121 or 365(c). (35 U.S.C. 154(a)(2) does not take into account, for the determination of the patent term, any application on which priority is claimed under 35 U.S.C. 119, 365(a) or 365(b).) For a c-i-p application, applicant should review whether any claim in the patent that will issue is supported by an earlier application and, if not, the applicant should consider canceling the reference to the earlier filed application. The term of a patent is not based on a claim-by-claim approach. See Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,205.*

**WARNING:** *When the last day of pendency of a provisional application falls on a Saturday, Sunday, or Federal holiday within the District of Columbia, any nonprovisional application claiming benefit of the provisional application must be filed prior to the Saturday, Sunday, or Federal holiday within the District of Columbia. See 37 C.F.R. § 1.78(a)(3).*

- The new application being transmitted claims the benefit of prior U.S. application(s).

### 3. Papers Enclosed

**A. Required for Filing Date under 37 C.F.R. 1.53(b) (Regular) or 37 C.F.R. 1.153 (Design) Application**

50 Pages of Specification  
21 Pages of Claims  
0 Sheets of Drawing

[ ] Formal  
[ ] Informal

**B. Other Papers Enclosed**

1 Pages of Abstract  
\_\_\_\_ Other

**WARNING:** *DO NOT submit original drawings. A high quality copy of the drawings should be supplied when filing a patent application. The drawings that are submitted to the Office must be on strong, white, smooth, and non-shiny paper and meet the standards according to § 1.84. If corrections to the drawings are necessary, they should be made to the original drawing and a high-quality copy of the corrected original drawing then submitted to the Office. Only one copy is required or desired. For comments on proposed then-new 37 C.F.R. 1.84, see Notice of March 9, 1988 . . . (1990 O.G. 57-62).*

**NOTE:** *"Identifying indicia, if provided, should include the application number or the title of the invention, inventor's name, docket number (if any), and the name and telephone number of a person to call if the Office is unable to match the drawings to the proper application. This information should be placed on the back of each sheet of drawing a minimum distance of 1.5 cm. (5/8 inch) down from the top of the page." 37 C.F.R. 1.84(c)).*

*(complete the following, if applicable)*

- [ ] The enclosed drawing(s) are photograph(s), and there is also attached a "PETITION TO ACCEPT PHOTOGRAPH(S) AS DRAWING(S)." 37 C.F.R. 1.84(b).

#### 4. Additional Papers Enclosed

- [ ] Preliminary Amendment
- [ ] Information Disclosure Statement (37 C.F.R. 1.98)
- [ ] Form PTO-1449 (PTO/SB/08A and 08B)
- [ ] Citations
- [ ] Declaration of Biological Deposit
- [ ] Submission of "Sequence Listing," computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.
- [ ] Authorization of Attorney(s) to Accept and Follow Instructions from Representative
- [ ] Special Comments
- [ ] Other

#### 5. Declaration or Oath

**NOTE:** *A newly executed declaration is not required in a continuation or divisional application provided the prior nonprovisional application contained a declaration as required, the application being filed is by all or fewer than all the inventors named in the prior application, there is no new matter in the application being filed, and a copy of the executed declaration filed in the prior application (showing the signature or an indication thereon that it was signed) is submitted. The copy must be accompanied by a statement requesting deletion of the names of person(s) who are not inventors of the application being filed. If the declaration in the prior application was filed under § 1.47 then a copy of that declaration must be filed accompanied by a copy of the decision granting § 1.47 status or, if a nonsigning person under § 1.47 has subsequently joined in a prior application, then a copy of the subsequently executed declaration must be filed. See 37 CFR 1.63(d).*

**NOTE:** *A declaration filed to complete an application must be executed, identify the specification to which it is directed, identify each inventor by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and the residence, post office address and country of citizenship of each inventor and state whether the inventor is a sole or joint inventor. 37 CFR 1.63(a)(1)-(4).*

- [ ] Enclosed

Executed by

*(check all applicable boxes)*

- [ ] inventor(s).
- [ ] legal representative of inventor(s). 37 CFR 1.42 or 1.43.
- [ ] joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached.
- [ ] This is the petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 is also attached. See item 13 below for fee.

- [X] Not Enclosed.

**NOTE:** *Where the filing is a completion in the U.S. of an International Application, or where the completion of the U.S. application contains subject matter in addition to the International Application, the application may be treated as a*

*continuation or continuation-in-part, as the case may be, utilizing ADDED PAGE FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION CLAIMED.*

- Application is made by a person authorized under 37 C.F.R. 1.41(c) on behalf of all the above named inventor(s).

*(The declaration or oath, along with the surcharge required by 37 CFR 1.16(e), can be filed subsequently).*

*NOTE: It is important that all the correct inventor(s) are named for filing under 37 CFR 1.41(c) and 1.53(b).*

- Showing that the filing is authorized.  
*(not required unless called into question. 37 CFR 1.41(d))*

## 6. Inventorship Statement

**WARNING:** *If the named inventors are each not the inventors of all the claims an explanation, including the ownership of the various claims at the time the last claimed invention was made, should be submitted.*

The inventorship for all the claims in this application are:

- The same.  
**or**  
 Not the same. An explanation, including the ownership of the various claims at the time the last claimed invention was made,  
 is submitted.  
 will be submitted.

## 7. Language

*NOTE: An application including a signed oath or declaration may be filed in a language other than English. An English translation of the non-English language application and the processing fee of \$130.00 required by 37 CFR 1.17(k) is required to be filed with the application, or within such time as may be set by the Office. 37 CFR 1.52(d).*

- English  
 Non-English

- The attached translation includes a statement that the translation is accurate. 37 C.F.R. 1.52(d).

## 8. Assignment

- An assignment of the invention to Cambridge NeuroScience, Inc.  
One Kendall Square, Building 700, Cambridge, Massachusetts 02139

- is attached. A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

[ ] was filed in the parent application

[X] will follow.

*NOTE: "If an assignment is submitted with a new application, send two separate letters-one for the application and one for the assignment" Notice of May 4, 1990 (1114 O.G. 77-78).*

*WARNING: A newly executed "STATEMENT UNDER 37 CFR 3.73(b)" must be filed when a continuation-in-part application is filed by an assignee. Notice of April 30, 1993, 1150 O.G. 62-64.*

## 9. Certified Copy

Certified copy(ies) of application(s)

<u>Country</u>	<u>Appln. No.</u>	<u>Filed</u>
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from which priority is claimed

[ ] is (are) attached.

[ ] will follow.

*NOTE: The foreign application forming the basis for the claim for priority must be referred to in the oath or declaration. 37 CFR 1.55(a) and 1.63.*

*NOTE: This item is for any foreign priority for which the application being filed directly relates. If any parent U.S. application or International Application from which this application claims benefit under 35 U.S.C. 120 is itself entitled to priority from a prior foreign application, then complete item 18 on the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.*

## 10. Fee Calculation (37 C.F.R. 1.16)

A. [X] Regular application

CLAIMS AS FILED					
Claims	Number Filed	Basic Fee Allowance	Number Extra	Rate	Basic Fee 37 C.F.R. 1.16(a) <b>\$790.00</b>
<b>Total Claims (37 CFR 1.16(c))</b>		- 20 =	x	\$ 22.00	\$0.00
<b>Independent Claims (37 CFR 1.16(b))</b>		- 3 =	x	\$82.00	\$0.00
<b>Multiple Dependent Claim(s), if any (37 CFR 1.16(d))</b>			+	\$270.00	

- Amendment cancelling extra claims is enclosed.
- Amendment deleting multiple-dependencies is enclosed.
- Fee for extra claims is not being paid at this time.

*NOTE: If the fees for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the Patent and Trademark Office in any notice of fee deficiency. 37 CFR 1.16(d).*

Filing Fee Calculation      \$ 790.00

- B.  Design application  
(\$330.00—37 CFR 1.16(f))

Filing Fee Calculation      \$ \_\_\_\_\_

- C.  Plant application  
(\$540.00—37 CFR 1.16(g))

Filing Fee Calculation      \$ \_\_\_\_\_

## 11. Small Entity Statement(s)

- Statement(s) that this is a filing by a small entity under 37 CFR 1.9 and 1.27 is (are) attached.

**WARNING:** *"Status as a small entity must be specifically established in each application or patent in which the status is available and desired. Status as a small entity in one application or patent does not affect any other application or patent, including applications or patents which are directly or indirectly dependent upon the application or patent in which the status has been established. The refiling of an application under § 1.53 as a continuation, division, or continuation-in-part (including a continued prosecution application under § 1.53(d)), or the filing of a reissue application requires a new determination as to continued entitlement to small entity status for the continuing or reissue application. A nonprovisional application claiming benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) of a prior application, or a reissue application may rely on a statement filed in the prior application or in the patent if the nonprovisional application or the reissue application includes a reference to the statement in the prior application or in the patent or includes a copy of the statement in the prior application or in the patent and status as a small entity is still proper and desired. The payment of the small entity basic statutory filing fee will be treated as such a reference for purposes of this section." 37 CFR 1.28(a)(2).*

*(complete the following, if applicable)*

- Status as a small entity was claimed in prior application  
60/064,826, filed on October 17, 1997 from which benefit is being claimed for this application under:

35 U.S.C. §      [X]      119(e),  
                  [ ]      120,  
                  [ ]      121,  
                  [ ]      365(c),

and which status as a small entity is still proper and desired.

- A copy of the statement in the prior application is included.

Filing Fee Calculation (50% of A, B or C above) \$ \_\_\_\_\_

*NOTE: Any excess of the full fee paid will be refunded if a small entity status is established refund request are filed within 2 months of the date of timely payment of a full fee. The two-month period is not extendable under § 1.136. 37 CFR 1.28(a).*

**12. Request for International-Type Search (37 C.F.R. 1.104(d))**

*(complete, if applicable)*

- [ ] Please prepare an international-type search report for this application at the time when national examination on the merits takes place.

**13. Fee Payment Being Made at This Time**

- [X] Not Enclosed

- [X] No filing fee is to be paid at this time.

*(This and the surcharge required by 37 C.F.R. 1.16(e) can be paid subsequently.)*

- [ ] Enclosed

[ ] Filing fee \$ \_\_\_\_\_

[ ] Recording assignment  
(\$40.00; 37 C.F.R. 1.21(h))  
(See attached "COVER SHEET FOR  
ASSIGNMENT ACCOMPANYING NEW  
APPLICATION.") \$ \_\_\_\_\_

[ ] Petition fee for filing by other than  
all the inventors or person on behalf  
of the inventor where inventor  
refused to sign or cannot be reached  
(\$130.00; 37 C.F.R. 1.47 and 1.17(i)) \$ \_\_\_\_\_

[ ] For processing an application with a  
specification in a non-English language  
(\$130.00; 37 C.F.R. 1.52(d) and 1.17(k)) \$ \_\_\_\_\_

[ ] Processing and retention fee  
(\$130.00; 37 C.F.R. 1.53(d) and 1.21(l)) \$ \_\_\_\_\_

[ ] Fee for international-type search report  
(\$40.00; 37 C.F.R. 1.21(e)) \$ \_\_\_\_\_

*NOTE: 37 CFR 1.21(l) establishes a fee for processing and retaining any application that is abandoned for failing to complete the application pursuant to 37 CFR 1.53(f) and this, as well as the changes to 37 CFR 1.53 and 1.78(a)(1), indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be paid, or the processing and retention fee of § 1.21(l) must be paid, within 1 year from notification under § 53(f).*

Total Fees Enclosed \$ \_\_\_\_\_

**14. Method of Payment of Fees**

- Check in the amount of \$\_\_\_\_\_.
- Charge Account No. \_\_\_\_\_ in the amount of \$\_\_\_\_\_.  
A duplicate of this transmittal is attached.

*NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 CFR 1.22(b).*

**15. Authorization to Charge Additional Fees**

**WARNING:** *If no fees are to be paid on filing, the following items should not be completed.*

**WARNING:** *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges, if extra claim charges are authorized.*

- The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Account No.\_\_\_\_\_.
- 37 C.F.R. 1.16(a), (f) or (g) (filing fees)  
 37 C.F.R. 1.16(b), (c) and (d) (presentation of extra claims)

*NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.*

- 37 C.F.R. 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)  
 37 CFR 1.17(a)(1)-(5) (extension fees pursuant to § 1.136(a)).  
 37 C.F.R. 1.17 (application processing fees)

*NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 CFR 1.136(a)(3).*

- 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

*NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 CFR 1.311(b)).*

*NOTE: 37 CFR 1.28(b) requires "Notification of any change in status resulting in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying, . . . issue fee." From the wording of 37 CFR 1.28(b), (a)*

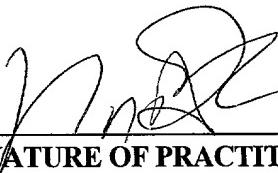
*notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.*

## 16. Instructions as to Overpayment

*NOTE: ". . . Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 CFR 1.26(a).*

[X] Credit Account No. 04-1105.

[ ] Refund



**SIGNATURE OF PRACTITIONER**

Peter F. Corless

(*type or print name of practitioner*)

Dike, Bronstein, Roberts & Cushman, LLP

130 Water Street

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Customer No.:

Docket No. 47578  
Express Mail Label No. EL014417763US

PHARMACEUTICALLY ACTIVE COMPOUNDS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part of U.S. provisional application 60/064,830, filed October 21, 1997, which application is incorporated herein by reference in its entirety.

5

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to pharmaceutically active compounds, including acylguanidine compounds, and methods of treatment and 10 pharmaceutical compositions that utilize or comprise one or more such compounds. Compounds of the invention are particularly useful for the treatment or prophylaxis of neurological injury and neurodegenerative disorders.

15 2. Background

Nerve cell death (degeneration) can cause potentially devastating and irreversible effects for an individual and may occur e.g. as a result of stroke, heart attack or other brain or spinal chord ischemia or trauma. Additionally, neurodegenerative disorders involve nerve cell death 20 (degeneration) such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Down's Syndrome and Korsakoff's disease.

Therapies have been investigated to treat nerve cell degeneration and 25 related disorders, e.g., by limiting the extent of nerve cell death that may otherwise occur to an individual. See, e.g., N. L. Reddy et al., *J. Med. Chem.*, 37:260-267 (1994); and WO 95/20950.

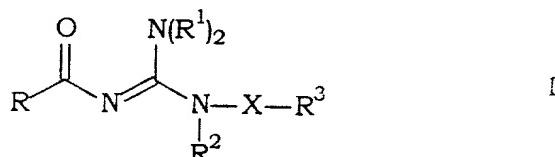
The compound MK-801 has exhibited good results in a variety of *in vivo* models of stroke. See B. Meldrum, *Cerebrovascular Brain Metab. Rev.*, 2:27-57 (1990); D. Choi, *Cerebrovascular Brain Metab. Rev.*, 2:105-147 (1990). See also Merck Index, monograph 3392, 11th ed., 1989. For example, MK-801 exhibits good activity in mouse audiogenic tests, a recognized model for evaluation of neuroprotective drugs. See, e.g., M. Tricklebank et al., *European Journal of Pharmacology*, 167:127-135 (1989); T. Seyfried, *Federation Proceedings*, 38(10):2399-2404 (1979).

However, MK-801 also has shown toxicity and further clinical development of the compound is currently uncertain. See J. W. Olney et al., *Science*, 244:1360-1362 (1989); W. Koek et al., *J. Pharmacol. Exp. Ther.*, 252:349-357 (1990); F.R. Sharp et al., *Society for Neuroscience Abstr.*, abstr. no. 482.3 (1992).

It thus would be highly desirable to have new neuroprotective agents, particularly agents to limit the extent or otherwise treat nerve cell death (degeneration) such as may occur with stroke, heart attack or brain or spinal cord trauma, or to treat neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Down's Syndrome and Korsakoff's disease.

#### SUMMARY OF THE INVENTION

In a first aspect, the present invention provides acylguanidine compounds of the following Formula I:

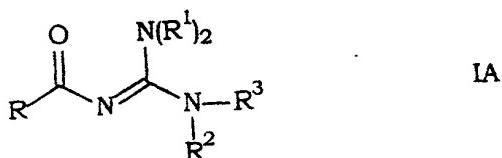


wherein R is an optionally substituted cyclic alkyl preferably having five or more carbon ring members; optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms; optionally substituted alkylaryl

- preferably having from 7 to about 18 carbon atoms; or optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms;
- each R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, optionally
- 5    substituted alkyl preferably having from 1 to about 20 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 3 carbon atoms; optionally substituted alkenyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 8 carbon atoms; optionally substituted alkynyl preferably having 2 to about 20 carbon atoms, more
- 10    preferably 2 to about 8 carbon atoms; optionally substituted alkoxy preferably having from 1 to about 20 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 3 carbon atoms; optionally substituted alkylthio preferably having from 1 to about 20 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to
- 15    about 3 carbon atoms; optionally substituted alkylsulfinyl preferably having from 1 to about 20 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 3 carbon atoms; optionally substituted alkylsulfonyl preferably having from 1 to about 20 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to
- 20    about 3 carbon atoms; optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms; or optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 hetero atoms;
- X is a chemical bond; optionally substituted alkylene, alkenylene or alkenylene linkage preferably having from 1 to about 6 carbons in the linkage, more preferably from 1 to 4 carbons in the linkage; or an optionally substituted heteroalkylene, heteroalkenylene heteroalkynylene linkage preferably having from 1 to about 6 carbons in the linkage, more preferably from 1 to 4 carbons in the linkage; and
- 25    R<sup>3</sup> is an optionally substituted cycloalkyl preferably having 3 or more carbon ring members, more preferably about 5 or more carbon ring members; optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms; optionally substituted alkylaryl preferably having from 7 to about 18 carbon atoms; or optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 ring members in each

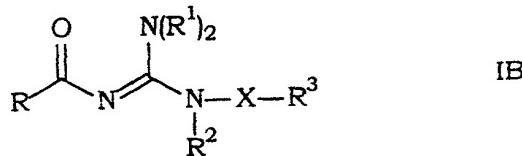
ring and from 1 to 3 hetero atoms; and pharmaceutically acceptable salts thereof.

In the above Formula I, X may suitably be a chemical bond, i.e.  
5 compounds of the following Formula IA:



wherein R, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each the same as defined above for Formula I; and pharmaceutically acceptable salts of those compounds.

10 It also has been found that compounds having X being an alkylene linkage, particularly C<sub>1-4</sub> alkylene, exhibit significant biological activity as shown in the examples which follow. Thus preferred are compounds of the following Formula IB:



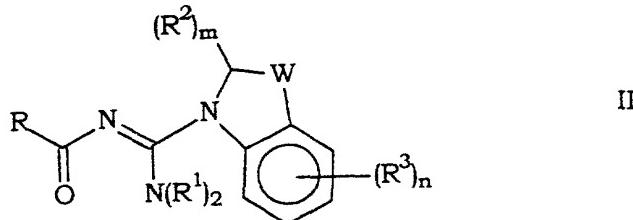
15 wherein X is an optionally substituted alkylene linkage preferably having from 1 to about 6 carbon atoms in the alkylene chain, more preferably 1 to 4 carbon atoms in the alkylene chain, and R, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each the same as defined above for Formula I; and pharmaceutically acceptable salts of those compounds.

Preferred compounds also include those of the above Formulae I, IA or IB wherein one or more of each R<sup>1</sup> and R<sup>2</sup> are hydrogen, including  
20 wherein each R<sup>1</sup> and R<sup>2</sup> are all hydrogen. Generally preferred R<sup>2</sup> groups of Formulae I, IA and IB include hydrogen and optionally substituted alkyl such as optionally substituted C<sub>1-6</sub> alkyl, or more preferably optionally

substituted C<sub>1-3</sub> alkyl. Preferred R<sup>3</sup> groups of Formula I, IA and IB include  
optionally substituted carbocyclic aryl or alkaryl such as optionally  
substituted phenyl, naphthyl and the like, and optionally substituted  
heteroalicyclic or heteroaromatic such as indolyl and the like, or optionally  
5 substituted cycloalkyl such as cyclohexyl and the like.

In a further aspect, the invention provides acylimine-substituted  
indolinyl-type compounds, particularly compounds of the following Formula  
II:

10



15

wherein R is an optionally substituted cyclic alkyl preferably having  
five or more carbon ring members; optionally substituted carbocyclic aryl  
having at least about 6 ring carbon atoms; optionally substituted alkylaryl  
preferably having from 7 to about 18 carbon atoms; or optionally  
substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings,  
3 to 8 ring members in each ring and from 1 to 3 hetero atoms;

R<sup>1</sup> is selected from the same group defined for R<sup>1</sup> and R<sup>2</sup> in  
Formula I;

20

each R<sup>2</sup> and each R<sup>3</sup> (i.e. substituent of the 4,5, 6 and 7 aromatic ring  
positions) are each independently hydrogen, halogen, hydroxyl, azido,  
optionally substituted alkyl preferably having from 1 to about 20 carbon  
atoms, optionally substituted alkenyl preferably having from 2 to about 20  
carbon atoms, optionally substituted alkynyl preferably having from 2 to  
25 about 20 carbon atoms, optionally substituted alkoxy preferably having  
from 1 to about 20 carbon atoms, optionally substituted alkylthio preferably  
having 1 to about 20 carbon atoms, optionally substituted alkylsulfinyl  
preferably having from 1 to about 20 carbon atoms, optionally substituted  
alkylsulfonyl preferably having from 1 to about 20 carbon atoms, optionally

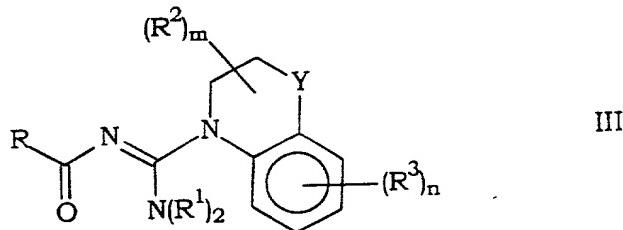
substituted aminoalkyl preferably having from 1 to about 20 carbon atoms, optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms, or optionally substituted aralkyl having at least about 6 ring carbon atoms;

- 5        W is optionally substituted methylene (-CH<sub>2</sub>-; i.e. indolinyl compounds), -S- (i.e. 3-benzothiazolinylcarboximidamide compounds), -O-, optionally substituted -N-, -S(O)- or -S(O<sub>2</sub>)-;  
m is 0, 1 or 2; n is 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts of those compounds.

- 10      In Formula II, generally preferred are compounds where W is optionally substituted methylene, i.e. indolinyl compounds. Optionally substituted phenyl, naphthyl, adamantyl and thiophenyl and other heteroaromatic groups are preferred R groups for compounds of Formula II.  
15      Preferred compounds of Formula II also include those where R<sup>1</sup> is hydrogen.

In a yet further aspect, the invention provides acylimine-substituted tetrahydroquinolinyl-type compounds, particularly compounds of the following Formula III:

20



- wherein R is an optionally substituted cyclic alkyl preferably having five or more carbon ring members; optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms; optionally substituted alkylaryl preferably having from 7 to about 18 carbon atoms; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 25      3 to 8 ring members in each ring and from 1 to 3 hetero atoms;

each R<sup>1</sup> is selected from the same group as defined for R<sup>1</sup> and R<sup>2</sup> in Formula I above;

each R<sup>2</sup> (i.e. substituent of the 2 and 3 ring positions) and each R<sup>3</sup> (i.e. substituent of the 5, 6, 7 and 8 aromatic ring positions) are each

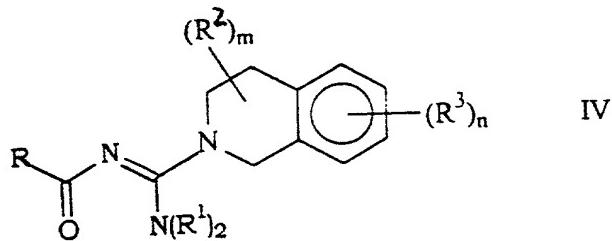
5 independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl preferably having from 1 to about 20 carbon atoms, optionally substituted alkenyl preferably having from 2 to about 20 carbon atoms, optionally substituted alkynyl preferably having from 2 to about 20 carbon atoms, optionally substituted alkoxy preferably having from 1 to about 20  
10 carbon atoms, optionally substituted alkylthio preferably having 1 to about 20 carbon atoms, optionally substituted alkylsulfinyl preferably having from 1 to about 20 carbon atoms, optionally substituted alkylsulfonyl preferably having from 1 to about 20 carbon atoms, optionally substituted aminoalkyl preferably having from 1 to about 20 carbon atoms, optionally substituted  
15 carbocyclic aryl having at least about 6 ring carbon atoms, or optionally substituted aralkyl having at least about 6 ring carbon atoms;

Y is optionally substituted methylene (-CH<sub>2</sub>-, i.e. 1,2,3,4-tetrahydroquinolinyl compounds), -O- (i.e. 2,3-benzmorpholinyl compounds), -S- (i.e. 2,3-benzthiomorpholinyl compounds), -S(O)-, -S(O<sub>2</sub>)-,  
20 or optionally substituted -N-,

m and n are each independently 0 (i.e. the available ring are each hydrogen-substituted), 1, 2, 3 or 4; and pharmaceutically acceptable salts of those compounds.

25 In Formula III, generally preferred are compounds where Y is methylene, i.e. 1,2,3,4-tetrahydroquinolinyl compounds. Optionally substituted phenyl and naphthyl are preferred R groups for compounds of Formula III. Preferred compounds of Formula III also include those where R<sup>1</sup> is hydrogen.

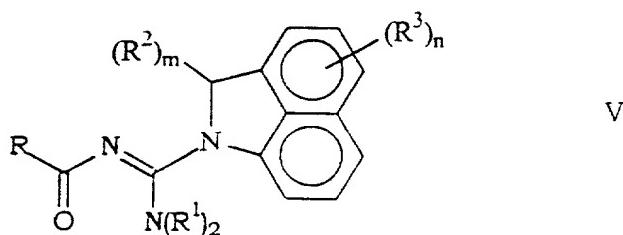
30 In a further aspect, the invention provide acylimine-substituted tetrahydroisoquinolinyl compounds, particularly compounds of the following Formula IV:



wherein R and each R<sup>1</sup> are the same as defined above for Formula I; each R<sup>2</sup> (i.e. substituent of the 1, 3 and 4 tetrahydroisoquinolinyl ring positions) and each R<sup>3</sup> (i.e. substituent of the 5, 6, 7 and 8 tetrahydroisoquinolinyl ring positions) are each independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl preferably having from 1 to about 20 carbon atoms, optionally substituted alkenyl preferably having from 2 to about 20 carbon atoms, optionally substituted alkynyl preferably having from 2 to about 20 carbon atoms, optionally substituted alkoxy preferably having from 1 to about 20 carbon atoms, optionally substituted alkylthio preferably having 1 to about 20 carbon atoms, optionally substituted alkylsulfinyl preferably having from 1 to about 20 carbon atoms, optionally substituted alkylsulfonyl preferably having from 1 to about 20 carbon atoms, optionally substituted aminoalkyl preferably having from 1 to about 20 carbon atoms, optionally substituted carbocyclic aryl suitably at least about 6 ring carbon atoms, or optionally substituted aralkyl suitably having at least about 6 ring carbon atoms;

m is 0 (i.e. the 1, 3 and 4 tetrahydroisoquinolinyl ring positions are each hydrogen-substituted), 1, 2, 3, 4, 5 or 6; n is 0 (i.e. the 5, 6, 7 and 8 tetrahydroisoquinolinyl ring positions are each hydrogen-substituted), 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

In another aspect, the invention provides compounds of the following Formula V:



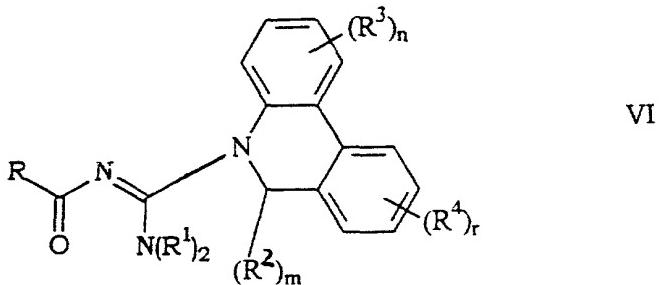
wherein R and each R<sup>1</sup> are the same as defined above for Formula I; each R<sup>2</sup> and each R<sup>3</sup> (i.e. substituent of the aromatic positions 3-8) are each independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl preferably having from 1 to about 20 carbon atoms,

5       optionally substituted alkenyl preferably having from 2 to about 20 carbon atoms, optionally substituted alkynyl preferably having from 2 to about 20 carbon atoms, optionally substituted alkoxy preferably having from 1 to about 20 carbon atoms, optionally substituted alkylthio preferably having 1 to about 20 carbon atoms, optionally substituted alkylsulfinyl preferably

10      having from 1 to about 20 carbon atoms, optionally substituted alkylsulfonyl preferably having from 1 to about 20 carbon atoms, optionally substituted aminoalkyl preferably having from 1 to about 20 carbon atoms, optionally substituted carbocyclic aryl suitably having at least about 6 ring carbon atoms, or optionally substituted aralkyl suitably having at least about 6 ring carbon atoms;

15      m is 0 (i.e. the 2-benz[cd]indolinyl position is hydrogen-substituted), 1 or 2; and n is 0 (i.e. the available ring are each hydrogen-substituted), 1, 2, 3, 4, 5 or 6; and pharmaceutically acceptable salts thereof.

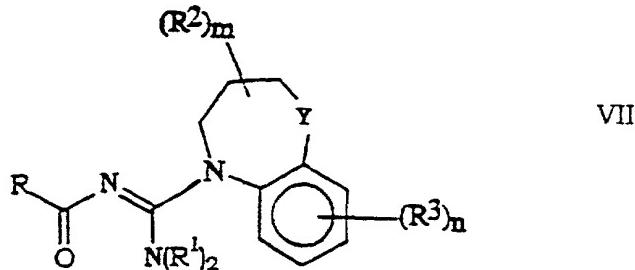
20       Still further, the invention provides compounds of the following Formula VI:



25       wherein R and each R<sup>1</sup> are the same as defined above for Formula I; each R<sup>2</sup>, each R<sup>3</sup> (i.e. substituent of the aromatic positions 1-4) and each R<sup>4</sup> (i.e. substituent of the aromatic positions 7-10) are each independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl preferably having from 1 to about 20 carbon atoms, optionally

- substituted alkenyl preferably having from 2 to about 20 carbon atoms, optionally substituted alkynyl preferably having from 2 to about 20 carbon atoms, optionally substituted alkoxy preferably having from 1 to about 20 carbon atoms, optionally substituted alkylthio preferably having 1 to about 5 20 carbon atoms, optionally substituted alkylsulfinyl preferably having from 1 to about 20 carbon atoms, optionally substituted alkylsulfonyl preferably having from 1 to about 20 carbon atoms, optionally substituted aminoalkyl preferably having from 1 to about 20 carbon atoms, optionally substituted carbocyclic aryl suitably having at least about 6 ring carbon atoms, or 10 optionally substituted aralkyl suitably having at least about 6 ring carbon atoms;
- 15 m is 0 (i.e. the 5,6-dihydrophenanthridinyl ring position is hydrogen-substituted), 1 or 2; and n and r are each independently 0 (i.e. the ring positions are each hydrogen-substituted), 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

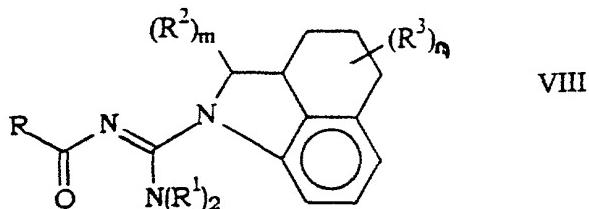
In an additional aspect, the invention provides compounds of the following Formula VII:



20

wherein R, each R<sup>1</sup>, Y, each R<sup>2</sup>, each R<sup>3</sup> and n are the same as defined above for Formula III; and m of Formula VII is an integer equal to 0-6, and preferably m is 0, 1 or 2; and pharmaceutically acceptable salts thereof.

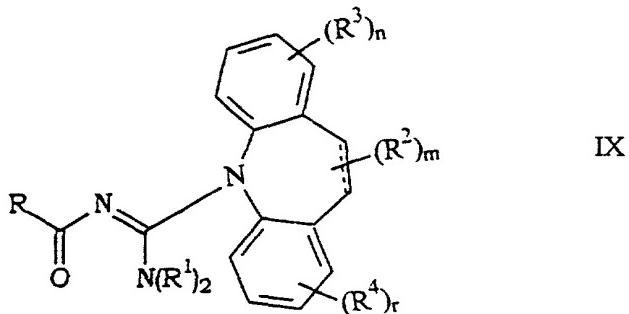
The invention also provides compounds of the following Formula VIII:



wherein R, each  $\text{R}^1$ , each  $\text{R}^2$ , each  $\text{R}^3$  and m are the same as defined above for Formula V; and n of Formula VIII is an integer equal to 0-9, and preferably n is 0, 1 or 2; and pharmaceutically acceptable salts thereof. It is understand that each  $\text{R}^3$  can be the same or different and may be present on either the non-aromatic or aromatic fused ring as depicted in the above structural formula.

10

The invention further provides compounds of the following Formula IX:

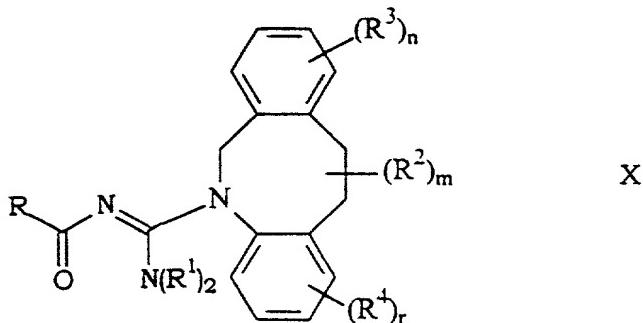


15

wherein R,  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ , n and r are the same as defined above for Formula VI, and m of Formula IX is an integer equal to 0-4, and preferably m is 0, 1 or 2, and the dotted line in Formula IX represents an optional carbon-carbon double bond (endocyclic bond); and pharmaceutically acceptable salts thereof.

20

In a further aspect, compounds of the following Formula X are provided:



wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, n and r are the same as defined above for Formula VI, and m of Formula X is an integer equal to 0-6 (i.e. R<sup>2</sup> may be a substituent at any of the available three saturated ring positions), and 5 preferably m is 0, 1 or 2; and pharmaceutically acceptable salts thereof.

In a further aspect, the invention also provides compounds of the Formulae I', IA', IB', II', III', IV', V', VI', VII', VIII', IX' and X', which formulae 10 are defined the same as Formulae I, IA, IB, II, III, IV, V, VI, VII, VIII, IX and X respectively, except that the substituent R may be selected from the group of an optionally substituted cyclic alkyl preferably having five or more carbon ring members; optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms; optionally substituted alkylaryl preferably 15 having from 7 to about 18 carbon atoms; or optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero (N, O or S) atoms; optionally substituted aralkyl preferably having from 7 to about 18 carbon atoms; optionally substituted heteroaralkyl preferably having from 5 to about 18 20 carbon atoms, and from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero (N, O or S) atoms; or optionally substituted heteroalicyclicalkyl preferably having from 5 to about 18 carbon atoms, and from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero (N, O or S) atoms. For such compounds of Formulae I', IA', IB', II', III', IV', 25 V', VI', VII', VIII', IX' and X', preferred R groups include optionally substituted aralkyl, particularly optionally substituted carbocyclic aralkyl such as optionally substituted phenalkyl, e.g. optionally substituted

phenyl(C<sub>1-8</sub>)alkyl, more typically optionally substituted phenyl(C<sub>1-6</sub>)alkyl, still more typically optionally substituted phenyl(C<sub>1-4</sub>)alkyl such as an optionally substituted phenacetyl (C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>C(=O)) group and the like. Additional particularly suitable R groups of such compounds of Formulae I', IA', IB', II', III', IV', V', VI', VII', VIII', IX' and X' include optionally substituted heteroaryalkyl and optionally substituted heteroalicyclicalkyl, such as optionally substituted heteroaryl(C<sub>1-8</sub>)alkyl or heteroalicyclic(C<sub>1-8</sub>)alkyl, more typically optionally substituted heteroaryl(C<sub>1-6</sub>)alkyl or heteroalicyclic(C<sub>1-6</sub>)alkyl, still more typically optionally substituted heteroaryl(C<sub>1-4</sub>)alkyl or heteroalicyclic(C<sub>1-4</sub>)alkyl. It also should be understood that preferred substituents as disclosed herein of compounds of Formula I, IA, IB, II, III, IV, V, VI, VII, VIII, IX and X are also preferred substituents of the corresponding Formulae I', IA', IB', II', III', IV', V', VI', VII', VIII', IX' and X', unless indicated otherwise.

Compounds of the invention (i.e. compounds of Formulae I, IA, IB, II, III, IV, V, VI, VII, VIII, IX and X as well as compounds of Formulae I', IA', IB', II', III', IV', V', VI', VII', VIII', IX' and X') are useful for a number of therapeutic applications. In particular, the invention includes methods for treatment and/or prophylaxis of neurological conditions/injuries such as epilepsy, neurodegenerative conditions and/or nerve cell death (degeneration) resulting from or associated with e.g. hypoxia, hypoglycemia, brain or spinal chord ischemia, retinal ischemia, brain or spinal chord trauma or post-surgical neurological deficits and the like as well as neuropathic pain. The invention also includes methods for treating peripheral neuropathy. The compounds of the invention are especially useful for treatment of a person susceptible or suffering from stroke or heart attack or neurological deficits relating to cardiac arrest, a person suffering or susceptible to brain or spinal cord injury, or a person suffering from the effects of retinal ischemia or degeneration, or a person suffering from decreased blood flow or nutrient supply to retinal tissue or optic nerve, retinal trauma, glaucoma or optic nerve injury. Compounds of the invention also are useful to treat and/or prevent various neurodegenerative diseases such as Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Alzheimer's disease,

- Down's Syndrome, Korsakoff's disease, cerebral palsy and/or age-dependent dementia. Compounds of the invention will be further useful to treat and/or prevent migraines, shingles (herpes zoster), epilepsy, emesis and/or narcotic withdrawal symptoms. Compounds of the invention will be useful
- 5 for treatment of various types of pain, including e.g. chronic pain. The treatment methods of the invention in general comprise administration of a therapeutically effective amount of one or more compounds of the invention to an animal, including a mammal, particularly a human. Particularly preferred compounds of the invention exhibit good activity in an
- 10 anticonvulsant *in vivo* mouse audiogenic assay e.g. as disclosed in Example 11 which follows, preferably about 20% or more inhibition at a dose of a compound of the invention of 20 mg/kg, more preferably about 50% or more inhibition at a dose of 20 mg/kg in such an anticonvulsant *in vivo* audiogenic assay.
- 15
- The invention also provides pharmaceutical compositions that comprise one or more compounds of the invention and a suitable carrier for the compositions.
- 20 Other aspects of the invention are disclosed *infra*.

#### DETAILED DESCRIPTION OF THE INVENTION

We have now discovered that compounds of the above-defined Formulae I (which includes Formulae IA and IB), II, III, IV, V, VI, VII, VIII, IX and X as well as Formulae I', IA', IB', II', III', IV', V', VI', VII', VIII', IX' and X' are useful for therapeutic applications, including to treat neurological injury or a neurodegenerative disorder.

Suitable halogen substituent groups of compounds of Formulae I, IA,  
30 IB, II, III, IV, V, VI, VII, VIII, IX and X as well as Formulae I', IA', IB', II', III', IV', V', VI', VII', VIII', IX' and X'' as defined above (i.e. compounds of the invention) include F, Cl, Br and I. Alkyl groups of compounds of the invention typically have from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms,

even more preferably 1, 2, 3 or 4 carbon atoms, or still more preferably 1, 2 or 3 carbon atoms. As used herein, the term alkyl unless otherwise modified refers to both cyclic and noncyclic groups, although of course cyclic groups will comprise at least three carbon ring members. Preferred  
5 alkenyl and alkynyl groups of compounds of the invention have one or more unsaturated linkages and typically from 2 to about 12 carbon atoms, more preferably 2 to about 8 carbon atoms, still more preferably 2 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4 carbon atoms. The terms alkenyl and alkynyl as used herein refer to both cyclic and noncyclic groups,  
10 although straight or branched noncyclic groups are generally more preferred. Preferred alkoxy groups of compounds of the invention include groups having one or more oxygen linkages and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4 carbon atoms.  
15 Preferred alkylthio groups of compounds of the invention include those groups having one or more thioether linkages and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylthio groups having 1, 2, 3 or 4 carbon atoms are particularly preferred. Preferred  
20 alkylsulfinyl groups of compounds of the invention include those groups having one or more sulfoxide (SO) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfinyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred. Preferred alkylsulfonyl groups of  
25 compounds of the invention include those groups having one or more sulfonyl (SO<sub>2</sub>) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfonyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred. Preferred aminoalkyl groups include those groups  
30 having one or more primary, secondary and/or tertiary amine groups, and from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4 carbon atoms. Secondary and tertiary amine groups are generally more preferred than primary amine moieties. Suitable

heteroaromatic groups of compounds of the invention contain one or more N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, oxidizolyl, triazole, imidazolyl, indolyl, 5 benzofuranyl and benzothiazol. Suitable heteroalicyclic groups of compounds of the invention contain one or more N, O or S atoms and include, e.g., tetrahydrofuranyl, thienyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolindinyl groups. Suitable carbocyclic aryl groups of compounds of the invention include single and multiple ring compounds, 10 including multiple ring compounds that contain separate and/or fused aryl groups. Typical carbocyclic aryl groups of compounds of the invention contain 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms. Specifically preferred carbocyclic aryl groups include phenyl; naphthyl including 1-naphthyl and 2-naphthyl; biphenyl; phenanthryl; 15 anthracyl; and acenaphthyl. Substituted carbocyclic groups are particularly suitable including substituted phenyl, such as 2-substituted phenyl, 3-substituted phenyl, 4-substituted phenyl, 2,3-substituted phenyl, 2,5-substituted phenyl, 2,3,5-substituted and 2,4,5-substituted phenyl; and substituted naphthyl, including naphthyl substituted at the 5, 6 and/or 7 20 positions. Preferred substituents of such substituted carbocyclic groups are identified below.

Suitable aralkyl groups of compounds of the invention include single and multiple ring compounds, including multiple ring compounds that 25 contain separate and/or fused aryl groups. Typical aralkyl groups contain 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms. Preferred aralkyl groups include benzyl and methylenenaphthyl (-CH<sub>2</sub>-naphthyl), and other carbocyclic aralkyl groups, as discussed above.

30 Suitable heteroaralkyl groups of compounds of the invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused heteroaryl groups, where such groups are substituted onto an alkyl linkage. More preferably, a heteroaralkyl group contains a heteroaryl group that has 1 to 3 rings, 3 to 8 ring members

in each ring and from 1 to 3 hetero (N, O or S) atoms, substituted onto an alkyl linkage. Suitable heteroaryl groups substituted onto an alkyl linkage include e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, 5 oxazolyl, oxidizolyl, triazole, imidazolyl, indolyl, benzofuranyl and benzothiazol, as well as such groups fused to one or more benzene rings.

Suitable heteroalicyclicalkyl groups of compounds of the invention include single and multiple ring compounds, where such groups are 10 substituted onto an alkyl linkage. More preferably, a heteroallicralkyl group contains at least one ring that has 3 to 8 ring members from 1 to 3 hetero (N, O or S) atoms, substituted onto an alkyl linkage. Suitable heteroalicyclic groups substituted onto an alkyl linkage include e.g. tetrahydrofuranyl, thienyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolindinyl 15 groups.

As discussed above, X groups of Formula I and I' suitably are alkylene or heteroalkylene linkages, or may contain one or more carbon-carbon double or triple bonds, i.e. alkenylene, alkynylene, heteroalkenylene 20 or heteroalkynylene linkage. Such unsaturated X groups typically contain 1, 2, 3 or 4 carbon-carbon multiple bonds, more typically 1 or 2 carbon-carbon multiple bonds. An X group that is heteroalkylene, heteroalkenylene or heteroalkynylene contains one or more N, O or S atoms in the chain between amino group and R<sup>3</sup> group of Formula I or I', with other atoms in 25 the chain suitably being carbons. Typically a heteroalkylene, heteroalkenylene or heteroalkynylene X group contains 1-3 N, O or S atoms in the chain, more typically 1 or 2 N, O or S atoms. Typically an X group contains from about 1 to 6 carbon atoms.

30 Suitable cyclic alkyl R groups of Formulae I-X and I'-X' and R<sup>3</sup> groups of Formulae I, IA, IB, I', IA' and IB' include groups having five or six or more ring carbon atoms, particularly optionally substituted adamanyl, isobornyl, norbornyl, cyclohexyl, cyclopentyl and the like. Generally preferred cyclic

alkyl groups have from 5 to about 10 ring members. Cyclic alkyl groups having bridged structures, such as adamantyl, are particularly preferred.

- Generally preferred R<sup>1</sup> groups of Formulae I through X and I' through 5 X' include hydrogen and alkyl such as C<sub>1-6</sub> alkyl, more preferably alkyl having 1, 2 or 3 carbon atoms. Suitable compounds also include those where both R<sup>1</sup> of a compound are hydrogen, or where at least one R<sup>1</sup> group is hydrogen.
- 10 As discussed above, R, R<sup>1</sup>, X, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X, Y and W groups of compound of the invention are optionally substituted. A "substituted" R, R<sup>1</sup>, X, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X, Y and W group or other substituent may be substituted at one or more available positions, typically 1 to 3 or 4 positions, by one or more suitable groups such as those disclosed herein. Suitable groups that 15 may be present on a "substituted" R, R<sup>1</sup>, X, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, Y and W group or other substituent include e.g. halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; alkanoyl such as a C<sub>1-6</sub> alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms and 20 more preferably 1-3 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms; alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms or 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups 25 including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl 30 linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; carbocyclic aryl having 6 or more carbons, particularly phenyl (e.g. an R

group being a substituted or unsubstituted biphenyl moiety); and aralkyl such as benzyl.

Generally preferred substituents of "substituted" nitrogen and  
5 methylene W and Y groups of compounds of Formulae II, III, VII, II', III', and  
VII' include substituted and unsubstituted alkyl, including C<sub>1-4</sub> alkyl and  
halo-substituted C<sub>1-4</sub> alkyl, particularly fluoro-substituted C<sub>1-4</sub> alkyl such as  
trifluoromethyl, and in the case of a substituted methylene group, halogen  
and alkylthio.

10

Preferred carbocyclic ring substituents of compounds of the invention include halogen (F, Cl, Br and I; hydroxyl; azido; optionally substituted alkyl having 1 to about 6 carbons such as methyl, ethyl, propyl and butyl and branched groups such as isopropyl, sec-butyl and tert-butyl, and including  
15 halogenated alkyl, particularly fluoro-alkyl having 1 to about 6 carbon atoms; optionally substituted alkoxy having 1 to about 6 carbons such as methoxy, ethoxy, propoxy and butoxy, and including halogenated alkoxy, particularly fluoro-alkoxy having 1 to about 6 carbon atoms; optionally substituted alkylthio having 1 to about 6 carbons such as methylthio and  
20 ethylthio; optionally substituted alkylsulfinyl having 1 to about 6 carbons such as methylsulfinyl (-S(O)CH<sub>3</sub>) and ethylsulfinyl (-S(O)CH<sub>2</sub>CH<sub>3</sub>); optionally substituted alkylsulfonyl having 1 to about 6 carbons such as methylsulfonyl (-S(O)<sub>2</sub>CH<sub>3</sub>) and ethylsulfonyl (-S(O)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); and optionally substituted arylalkoxy such as benzyloxy (C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>O-).

25

It should be understood that alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl and aminoalkyl substituent groups described above include groups where a hetero atom is directly bonded to a ring system, such as a carbocyclic aryl group or a heterocyclic group, as well as groups where a  
30 hetero atom of the group is spaced from such ring system by an alkylene linkage, e.g. of 1 to about 4 carbon atoms.

Also, in the above Formulae I through X and I' through X', additional preferred groups that may be R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> as those substituent groups are

defined above, include optionally substituted sulfonamide, optionally substituted urea and optionally substituted thioamide.

Without wishing to be bound by theory, compounds of the invention  
5 that contain an alkylsulfinyl and/or alkylsulfonyl group, may be, in effect,  
"pro-drugs" wherein after administration of the compound to a subject the  
sulfinyl or sulfonyl group(s) are metabolized (reduced) *in vivo* to the  
corresponding sulfide moiety.

10 Specifically preferred compounds of the invention include the  
following:

N-(4-methylbenzoyl)- N'-methyl-N'-(3-methylthiophenyl)guanidine;  
N-(4-methylbenzoyl)-N'-methyl-N'-(3-iodophenylmethyl)guanidine;  
N-(4-methylbenzoyl)-N'-(1-naphthyl)guanidine;  
15 N-(4-methylbenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(4-methylbenzoyl)-N'-(4-tertbutylphenyl)guanidine;  
N-(4-methylbenzoyl)-1-indolinylcarboximidamide;  
N-(4-methylbenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(4-methylbenzoyl)-1-[7-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline]  
20 carboximidamide;  
N-(4-methylbenzoyl)-1-(1,2,3,4-tetrahydroquinoline)carboximidamide;  
N-(4-methylbenzoyl)-N'-(2,5-dibromophenyl)guanidine;  
N-(4-methylbenzoyl)-N'-(4-isopropoxyphenyl)guanidine;  
N-(4-methylbenzoyl)-N'-(3,4,5-trimethoxyphenyl)guanidine;  
25 N-(4-methylbenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(2,5-dichlorobenzoyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(2,5-dichlorobenzoyl)- N'-methyl-N'-(3-methylthiophenyl)guanidine;  
N-(2,5-dichlorobenzoyl)-N'-(1-naphthyl)guanidine;  
N-(2,5-dichlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
30 N-(2,5-dichlorobenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(2,5-dichlorobenzoyl)-N'-(4-tertbutylphenyl)guanidine;  
N-(2,5-dichlorobenzoyl)-1-indolinylcarboximidamide;  
N-(2,5-dichlorobenzoyl)- N'-methyl-N'-(4-isopropylphenyl)guanidine;  
N-(phenylacetyl)-N'-(4-benzyloxyphenyl)guanidine;

- N-(phenylacetyl)-N'-(4-isopropylphenyl)guanidine;  
N-(phenylacetyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(phenylacetyl)-1-indolinylcarboximidamide;  
N-(phenylacetyl)-1-(1,2,3,4-tetrahydroquinoline)carboximidamide;
- 5 N-(phenylacetyl)-N'-(4-isopropoxyphenyl)guanidine;  
N-(phenylacetyl)-N'-(4-isopropylphenyl)-N'-methylguanidine;  
N-(adamantan-1-carbonyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(adamantan-1-carbonyl)-N'-(1-naphthyl)guanidine;  
N-(adamantan-1-carbonyl)-N'-(4-benzyloxyphenyl)guanidine;
- 10 N-(adamantan-1-carbonyl)-N'-(4-isopropylphenyl)guanidine;  
N-(adamantan-1-carbonyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(adamantan-1-carbonyl)-1-(indolinyl)carboximidamide;  
N-(adamantan-1-carbonyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(adamantan-1-carbonyl)-N'-(2,5-dibromophenyl)guanidine;
- 15 N-(adamantan-1-carbonyl)-N'-(4-isopropylphenyl)-N'-methylguanidine;  
N-(4-chlorobenzoyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(4-chlorobenzoyl)-N'-methyl-N'-(3-methylthiophenyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(1-naphthyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;
- 20 N-(4-chlorobenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(4-chlorobenzoyl)-1-(indolinyl)carboximidamide;  
N-(4-chlorobenzoyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(4-chlorobenzoyl)-N'-(2,5-dibromophenyl)guanidine;
- 25 N-(3,4-dichlorobenzoyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(1-naphthyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(4-tert-butylphenyl)guanidine;
- 30 N-(3,4-dichlorobenzoyl)-1-(indolinyl)carboximidamide;  
N-(3,4-dichlorobenzoyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(3,4-dichlorobenzoyl)-N'-methyl-N'-(4-isopropylphenyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-methyl-N'-(3-methylthiophenyl)guanidine;

- N-(thiophen-2-carbonyl)-N'-(1-naphthyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(4-isopropylphenyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(4-tert-butylphenyl)guanidine;
- 5 N-(thiophen-2-carbonyl)-1-(indolinyl)carboximidamide;  
N-(thiophen-2-carbonyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(thiophen-2-carbonyl)-N'-methyl-N'-(4-isopropylphenyl)guanidine;  
N-(furan-2-carbonyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(furan-2-carbonyl)-N'-methyl-N'-(3-methylthiophenyl)guanidine;
- 10 N-(furan-2-carbonyl)-N'-(1-naphthyl)guanidine;  
N-(furan-2-carbonyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(furan-2-carbonyl)-N'-(4-isopropylphenyl)guanidine;  
N-(furan-2-carbonyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(furan-2-carbonyl)-1-(indolinyl)carboximidamide;
- 15 N-(furan-2-carbonyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(furan-2-carbonyl)-N'-(4-isopropylphenyl)-N'-methylguanidine;  
N-(pyridin-3-carbonyl)-N'-(1-naphthyl)guanidine;  
N-(pyridin-3-carbonyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(pyridin-3-carbonyl)-N'-(4-isopropylphenyl)guanidine;
- 20 N-(pyridin-3-carbonyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(pyridin-3-carbonyl)-1-(indolinyl)carboximidamide;  
N-(pyridin-3-carbonyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(4-methoxybenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(4-isopropylphenyl)guanidine;
- 25 N-(4-methoxybenzoyl)-N'-(4-isopropoxyphenyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(3,4,5-trimethoxyphenyl)guanidine;  
N-(1-naphthoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(1-naphthoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(1-naphthoyl)-N'-(4-isopropoxyphenyl)guanidine;
- 30 N-(3,4,5-trimethoxybenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(3,4,5-trimethoxybenzoyl)-N'-(4-isopropoxyphenyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(4-isopropoxyphenyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(3,4,5-trimethoxyphenyl)guanidine;

- N-(4-ethoxybenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(4-isopropoxyphenyl)guanidine;  
N-(4-methylbenzoyl)-N'-(benzyl)guanidine;  
N-(4-methylbenzoyl)-N'-(2-phenethyl)guanidine;  
5 N-(4-methylbenzoyl)-N'-(3-dimethylaminopropyl)guanidine;  
N-(4-methylbenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-methylbenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-methylbenzoyl)-N'-(1-naphthylmethyl)guanidine;  
N-(4-methylbenzoyl)-N'-(2-(4-chlorophenyl)ethyl)guanidine;  
10 N-(4-methylbenzoyl)-N'-(5-phenylpentyl)guanidine;  
N-(4-methylbenzoyl)-N'-(3-phenoxypropyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(benzyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(benzyl)guanidine;  
15 N-(4-chlorobenzoyl)-N'-(2-phenethyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(benzyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(3-dimethylaminopropyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(2-phenethyl)guanidine;  
20 N-(4-methoxybenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(2-(4-chlorophenylethyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(1-naphthylmethyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(3,4,5-trimethoxybenzyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(4-phenylbutyl)guanidine;  
25 N-(4-ethoxybenzoyl)-N'-(2-phenethyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(2-(4-chlorophenyl)ethyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(1-naphthylmethyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(4-phenylbutyl)guanidine;  
30 N-(4-butoxybenzoyl)-N'-(2-phenethyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(2-(4-chlorophenyl)ethyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(2-(3-indole)ethyl)guanidine;  
N-(3,4,5-trimethoxybenzoyl)-N'-(4-phenylbutyl)guanidine;

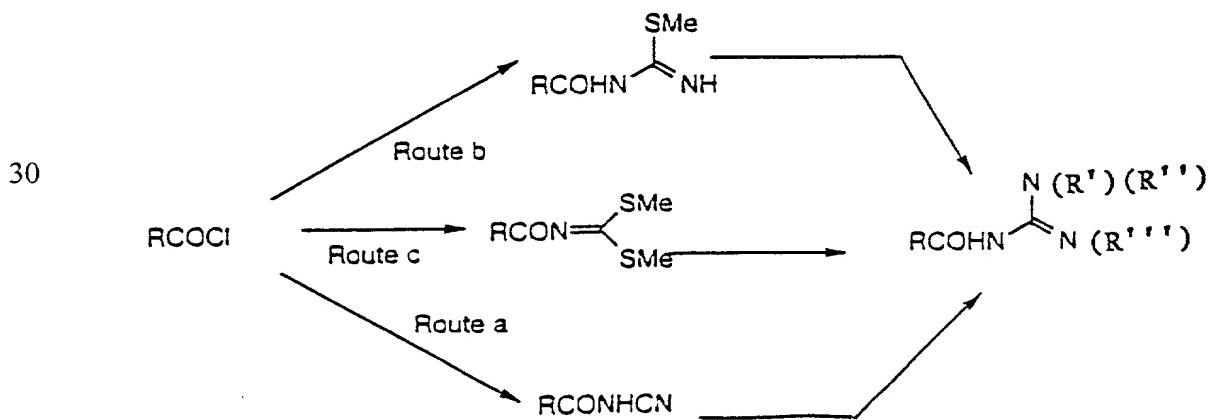
- N-(3,4,5-trimethoxybenzoyl)-N'-(2-(3-indole)ethyl)guanidine;  
N-(3,4,5-trimethoxybenzoyl)-N'-(2-phenylethyl)guanidine;  
N-(1-naphthoyl)-N'-(benzyl)guanidine;  
N-(1-naphthoyl)-N'-(3-dimethylaminopropyl)guanidine;
- 5 N-(1-naphthoyl)-N'-(2-phenylethyl)guanidine;  
N-(1-naphthoyl)-N'-(4-phenylbutyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(benzyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(3-dimethylaminopropyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(2-phenylethyl)guanidine;
- 10 N-(thiophen-2-carbonyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-methylbenzoyl)-N'-(cyclohexyl)-N''-methylguanidine;  
N-(4-methylbenzoyl)-N'-(4-phenylbutyl)-N''-methylguanidine;  
N-(4-methoxybenzoyl)-N'-(5-phenylpentyl)guanidine;  
N-(2-methylbenzoyl)-N'-(4-phenylbutyl)guanidine;
- 15 N-(2-methylbenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(2-methylbenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(2-methylbenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(2-phenoxypropyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(5-phenylpentyl)guanidine;
- 20 N-(4-methylbenzoyl)-N'-(2-phenoxyethyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(2-phenoxyethyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-[{(2-benzylthio)ethyl}guanidine];  
N-(4-ethoxybenzoyl)-N'-(3,4,5-trimethoxyphenyl)guanidine;  
and pharmaceutically acceptable salts thereof.
- 25 Additional specifically preferred compounds of the invention include the following:  
N-(2-methylbenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(2-methylbenzoyl)-N'-(4-isopropylphenyl)guanidine;
- 30 N-(4-ethoxybenzoyl)-N'-(3,4,5-trimethoxyphenyl)guanidine;  
N-benzoyl-N'-(4-isopropylphenyl)guanidine;  
N-benzoyl-N'-(4-isopropoxyphenyl)guanidine;  
N-benzoyl-N'-(4-benzyloxyphenyl)guanidine;  
N-benzoyl-N'-(2-isopropylphenyl)guanidine;

- N-(2,6-dichlorophenacetyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(2,6-dichlorophenacetyl)-N'-(phenyl)guanidine;  
N-(2,6-dichlorophenacetyl)-N'-(4-isopropyl)phenylguanidine;  
N-(2,6-dichlorophenacetyl)-1-(indolinyl)carboxamidamide;
- 5 N-(2-chlorobenzoyl)-N'-(4-isopropyl)phenylguanidine;  
N-(2-chlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(2-chlorobenzoyl)-1-(indolinyl)carboxamidamide;  
N-(2,6-dichlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(2,6-dichlorobenzoyl)-N'-(2-isopropylphenyl)guanidine;
- 10 N-(2,6-dichlorobenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(2,6-dichlorobenzoyl)-1-(indolinyl)carboxamidamide;  
N-(2,6-dichlorobenzoyl)-N'-(trimethoxyphenyl)guanidine;  
N-(2,3-dichlorobenzoyl)-N'-(4-isopropyl)phenylguanidine;  
N-(2,3-dichlorobenzoyl)-1-(indolinyl)carboxamidamide;
- 15 N-(2,3-dichlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(5-phenylpentyl)guanidine;  
N-(2-methylbenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(2-methylbenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(3-phenoxypropyl)guanidine;
- 20 N-(4-butoxybenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(3-phenoxyethyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(3-benzylthioethyl)guanidine;  
N-benzoyl-N'-(4-phenylbutyl)guanidine;  
N-benzoyl-N'-(3-phenoxypropyl)guanidine;
- 25 N-benzoyl-N'-(3,4,5-trimethoxybenzyl)guanidine;  
N-benzoyl-N'-(2-benzylthioethyl)guanidine;  
N-(4-methylbenzoyl)-N'-[[(indol-3-yl)-2-ethyl]guanidine];  
N-(4-chlorobenzoyl)-N'-[[(indol-3-yl)-2-ethyl]guanidine];  
N-(1-naphthoyl)-N'-[[(indol-3-yl)-2-ethyl]guanidine];
- 30 N-(thiophen-2-carbonyl)-N'-[[(indol-3-yl)-2-ethyl]guanidine];  
N-(4-methylbenzoyl)-N'-butylguanidine;  
N-(furan-2-carbonyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-methylbenzoyl)-N'-(2-benzylthioethyl)guanidine;  
N-(4-methylbenzoyl)-N'-(1-indanyl)guanidine;

- N-(N-(4-chlorobenzoyl)-N'-(1-indanyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(1-indanyl)guanidine;  
N-(1-naphthoyl)-N'-[imidazol-1-yl]-3-propyl]guanidine;  
N-(furan-2-carbonyl)-N'-[imidazol-1-yl]-3-propyl]guanidine;  
5 N-(4-chlorobenzoyl)-N'-(2-benzylthioethyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(2-benzylthioethyl)guanidine;  
N-(1-naphthoyl)-N'-(2-benzylthioethyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(2-benzylthioethyl)guanidine;  
N-(4-methylbenzoyl)-N'-(thiophen-2-yl)-2-ethyl]guanidine;  
10 N-(3,4-dichlorobenzoyl)-N'-(thiophen-2-yl)-2-ethyl]guanidine;  
N-(3,4,5-trimethoxybenzoyl)-N'-(thiophen-2-yl)-2-ethyl]guanidine;  
N-(furan-2-carbonyl)-N'-(thiophen-2-yl)-2-ethyl]guanidine;  
N-(thiophen-2-carbonyl)-N'-(thiophen-2-yl)-2-ethyl]guanidine;  
N-(2,3-dichlorobenzoyl)-N'-(4-phenylbutyl]guanidine;  
15 N-(2,5-dichlorobenzoyl)-N'-(4-phenylbutyl]guanidine;  
N-(2,6-dichlorobenzoyl)-N'-(4-phenylbutyl]guanidine;  
N-(2,6-dichlorophenylacetyl)-N'-benzylguanidine;  
N-(4-methylbenzoyl)-N'-(2-phenoxyethylguanidine;  
N-(benzoyl)-N'-(indol-3-yl-2-yl]guanidine;  
20 N-(1-naphthoyl)-N'-(4-chlorobenzyl)guanidine; and  
N-(3,4-dichlorobenzoyl)-N'-[imidazol-1-yl]-3-propyl]guanidine;  
and pharmaceutically acceptable salts thereof.

Compounds of the invention can be suitably prepared by one or more  
25 of several routes which are generally depicted in the following Scheme.

SCHEME



More specifically, as generally depicted in "Route a" above, compounds of the invention can be prepared by reaction of a suitable amine precursor compound with a suitable substituted cyanamide compound that 5 provides the desired R group of compounds of Formulae I through X as well as Formulae I' through X'.

Suitable amine precursor compounds include e.g. a substituted or unsubstituted aromatic amine, a substituted or unsubstituted arylalkylamine, 10 a substituted or unsubstituted indolinyl (or derivative thereof) compound to prepare compounds of Formula II or II', substituted or unsubstituted 1,2,3,4-tetrahydroquinolinyl (or derivative thereof) compound to prepare compounds of Formula III or III', or an optionally substituted benz[cd]indolinyl compound, optionally substituted 5,6- 15 dihydrophenanthridinyl compound, optionally substituted 2,3,4,5-tetrahydro-[1,5]-benzothiazepine compounds (or derivative thereof, e.g. where Y is other atom), 2a,3,4,5-tetrabenz[cd]indoline compound, 5,6,11,12-tetrahydroniben[b,f]azocine compound, etc. to prepare compounds of Formulae III through X as well as Formulae III' through X'. A secondary 20 amine can be employed to prepare compounds of Formulae I and I' where R<sup>2</sup> is other than hydrogen. For example, an N-methylaniline or other N-alkylaniline can be employed to provide an alkyl R<sup>2</sup> substituent for compounds of Formulae I and I'.

25 Suitable cyanamide compounds will include aryloylcyanamide compounds (i.e. aryl(C=O)NHCN) such as substituted or unsubstituted benzoylcyanamide and the like; an arylalkanoyl cyanamide such as substituted or unsubstituted phenylacetylcyanamide (C<sub>6</sub>H<sub>5</sub>COCH<sub>2</sub>NHCN) and the like; a cyclic alkanoyl cyanamide such as 30 adamantancarbonylcyanamide and the like; or a heteroaromatic(carbonyl)cyanamide or a heteroalicyclic(carbonyl)cyanamide such as (2-thiophenecarbonyl)cyanamide, (3- thiophenecarbonyl)cyanamide, (1- furanylcarbonyl)cyanamide, (2- furanylcarbonyl)cyanamide, (1- pyridylcarbonyl)cyanamide, (2- pyridylcarbonyl)cyanamide, (3-

pyridylcarbonyl)cyanamide, (1-tetrahydrofurylcarbonyl)cyanamide, (2-tetrahydrofurylcarbonyl)cyanamide and the like; or (for compounds of Formulae I' through X') an aralkyl, heteroaryl alkyl or heteroalicyclic alkyl reagent such as e.g. methyl phenylacetate and the like. See the examples which follow.

5

The cyanamide reactants can be readily prepared, e.g. by reaction of the corresponding substituted carbonylchloride reactant with cyanamide under suitable conditions, e.g. in the presence of base with stirring at room 10 temperature until reaction completion. The reaction solution with the thus formed substituted cyanamide then can be neutralized and the product isolated by standard procedures. See the Examples which follow for exemplary conditions.

15 Typically a salt (e.g. an HCl salt) of the amine precursor compound is reacted with the substituted cyanamide reagent. The amine precursor can be reacted with the substituted cyanamide reagent in a suitable solvent such as chlorobenzene, toluene or xylene with heating (e.g. reflux temperature) until reaction completion, e.g. 2 or more hours.

20

As generally depicted in "Route b" above, compounds of the invention also can be prepared by reaction of a substituted carbonylisothiourea (RCONHC(=NH)SCH<sub>3</sub> in above Route b) and a substituted amine precursor compound, typically a substituted aliphatic amine such as a 25 arylalkylamine, e.g. NH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>. This "Route b" is particularly suitable for synthesis of compounds of Formulae I or II where the substituent X is alkylene.

30 The isothiourea reagent can be readily prepared by reaction of S-methylisothiourea with a desired substituted carbonyl chloride such as a benzoyl chloride compound in the presence of base and in a suitable solvent such as aqueous diethyl ether at room temperature with stirring overnight. For exemplary conditions, see Example 5, Part I; Example 6, Part I; Example 7, Part I; and Example 8, Part I, which follow. The thus formed isothiourea

derivative is then reacted with the substituted amine in the presence of base such as triethylamine in a suitable solvent such as toluene, chlorobenzene or other aromatic solvent with heating, e.g. reflux temperature. See Example 5, Part I; Example 6, Part I; Example 7, Part I; and Example 8, Part 5 I, which follow for exemplary conditions.

As generally depicted in "Route c" above, compounds of the invention that contain an N"-substituent that is other than hydrogen (i.e. one or both of R<sup>1</sup> in Formulae I through X or Formulae I' through X' is other than 10 hydrogen) can be suitably prepared by reaction of a substituted carbimidodithiolate (RCON=C(SCH<sub>3</sub>)<sub>2</sub> in above Route c) and sequential reactions of substituted amine precursor compounds. The substituted carbimidodithiolate can be prepared by reaction of a desired substituted amide compound with carbon disulfide in a suitable solvent such as 15 tetrahydrofuran and in the presence of base such as sodium hydride. The isolated substituted carbimidodithiolate compound is reacted with a slight molar excess of a desired substituted amine (provides the desired R group). The resultant thiourea is further reacted with a substituted amine to provide N" substitution. See Example 9 which follows for exemplary 20 conditions.

As discussed above, the present invention includes methods for treating preventing certain neurological disorders, including the consequences of stroke, heart attack and traumatic head or brain injury, 25 epilepsy or neurodegenerative diseases comprising the administration of an effective amount of one or more compounds of the invention to a subject including a mammal, such as a primate, especially a human, in need of such treatment. In particular, the invention provides methods for treatment and/or prophylaxis of nerve cell death (degeneration) resulting e.g. from 30 hypoxia, hypoglycemia, brain or spinal cord ischemia, brain or spinal cord trauma, stroke, heart attack or drowning. Typical candidates for treatment include e.g. heart attack, stroke and/or persons suffering from cardiac arrest neurological deficits, brain or spinal cord injury patients, patients undergoing major surgery such as heart surgery where brain ischemia is a

potential complication and patients such as divers suffering from decompression sickness due to gas emboli in the blood stream. Candidates for treatment also will include those patients undergoing a surgical procedure involving extra-corporal circulation such as e.g. a bypass

5 procedure. Subjects suffering from or susceptible to peripheral necropathy can be treated in accordance with the invention by administration of an effective amount of one or more compounds of Formulae I through X or Formulae I' through X'.

10 The invention in particular provides methods for treatment which comprise administration of one or more compounds of the invention to a patient that is undergoing surgery or other procedure where brain or spinal cord ischemia is a potential risk. For example, carotid endarterectomy is a surgical procedure employed to correct atherosclerosis of the carotid arteries. Major risks associated with the procedure include intraoperative embolization and the danger of hypertension in the brain following increased cerebral blood flow, which may result in aneurism or hemorrhage. Thus, an effective amount of one or more compounds of the present invention could be administered pre-operatively or peri-operatively to reduce 15 such risks associated with carotid endarterectomy, or other post-surgical neurological deficits.

20 The invention further includes methods for prophylaxis against neurological deficits resulting from e.g. coronary artery bypass graft surgery and aortic valve replacement surgery, or other procedure involving extra-corporal circulation. Those methods will comprise administering to a patient undergoing such surgical procedures an effective amount of one or more compounds of the invention, typically either pre-operatively or peri-operatively.

25

The invention also provides methods for prophylaxis and treatment against neurological injury for patients undergoing myocardial infarction, a procedure that can result in ischemic insult to the patient. Such methods will comprise administering to a patient undergoing such surgical procedure

an effective amount of one or more compounds of the invention, typically either pre-operatively or peri-operatively.

Also provided are methods for treating or preventing neuropathic pain  
5 such as may experienced by cancer patients, persons having diabetes, amputees and other persons who may experience neuropathic pain. These methods for treatment comprise administration of an effective amount of one or more compounds of the invention to a patient in need of such treatment.

10

The invention also provides methods for treatment and prophylaxis against retinal ischemia or degeneration and resulting visual loss. For example, a compound of the invention can be administered parenterally or by other procedure as described herein to a subject a suffering from or  
15 susceptible to ischemic insult that may adversely affect retinal function, e.g., significantly elevated intraocular pressures, diseases such as retinal artery or vein occlusion, diabetes or other ischemic ocular-related diseases. Post-ischemic administration also may limit retinal damage. The invention also includes methods for treating and prophylaxis against decreased blood  
20 flow or nutrient supply to retinal tissue or optic nerve, or treatment or prophylaxis against retinal trauma or optic nerve injury. Subjects for treatment according to such therapeutic methods of the invention may be suffering or susceptible to retinal ischemia that is associated with atherosclerosis, venous capillary insufficiency, obstructive arterial or venous  
25 retinopathies, senile macular degeneration, cystoid macular edema or glaucoma, or the retinal ischemia may be associated with a tumor or injury to the mammal. Intravitreal injection of a compound of the invention also may be a preferred administration route to provide more direct treatment to the ischemic retina.

30

The invention also provides methods for treatment of a subject suffering from shingles as well as treatment of a person suffering from or susceptible to migraines, particularly to alleviate the pain and discomfort associated with those disorders. As discussed above, compounds of the

invention are also useful to treat persons suffering from various types of pain, including chronic pain. These methods comprise administration of an effective amount of one or more compounds of the invention to a patient in need of treatment.

5

The invention further provides a method of treating Korsakoff's disease, a chronic alcoholism-induced condition, comprising administering to a subject including a mammal, particularly a human, one or more compounds of the invention in an amount effective to treat the disease.

10 Compounds of the invention are anticipated to have utility for the attenuation of cell loss, hemorrhages and/or amino acid changes associated with Korsakoff's disease.

As discussed above, the invention also includes methods for treating 15 a person suffering from or susceptible to cerebral palsy, emesis, narcotic withdrawal symptoms and age-dependent dementia, comprising administering to a subject including a mammal, particularly a human, one or more compounds of the invention in an amount effective to treat the condition.

20

The invention also includes methods for treatment of infections, including Gram-negative and Gram-positive bacterial infections, comprising administering a combination of 1) an aminoglycoside antibiotic, and 2) a compound of Formulae I, IA, IB, II, III, IV, V, VI, VII, VIII, IX and/or X as well 25 as Formulae I', IA', IB', II', III', IV', V', VI', VII', VIII', IX' and/or X' as defined herein. A wide variety of aminoglycoside antibiotics are suitable for use in the formulations of the invention. Typically, suitable aminoglycoside antibiotics contain two or more amino sugars (aminoglycosides) connected to an amino-cyclitol nucleus. Exemplary aminoglycoside antibiotics 30 preferred for use in formulations of the present invention include clinical agents such as gentamycin, amikacin, kanamycin, streptomycin, paromocycin, neomycin, netilmicin and tobramycin. Other suitable aminoglycosides include seldomycins, sisomycins, aurimycin, lividomycins, streptothricins, hybrimycins, coralinomycin, butirosin, streptomutins,

nebramycins, tenebrimycins, ribostamycins, destomycins, trehalosamines, myomycins, fortimicins, mutamicins and kasugamycin. Suitable aminoglycoside antibiotics are also disclosed in U.S. Patents Nos. 5,508,269; 4,645,760; and 4,380,625. It should be appreciated however 5 that the present invention is not limited by any particular aminoglycoside antibiotic, and the invention is applicable to any aminoglycoside antibiotic now known or subsequently discovered or developed. The aminoglycoside and one or more compounds of the invention may be administered simultaneously, in the same or different pharmaceutical formulations, or 10 sequentially. Preferably, the components of the combination are administered substantially simultaneously, e.g. in a unitary pharmaceutical composition containing the two components. Preferred methods and compositions that comprise an aminoglycoside in combination with a compound of the invention will be effective against infections previously 15 treated with aminoglycoside antibiotics, but with the significant advantage of decreased occurrence of ototoxicity relative to use of an aminoglycoside antibiotic alone.

As discussed above, preferred compounds of the invention in a 20 standard anticonvulsant *in vivo* audiogenic test, such as the audiogenic mouse assay of Example 11 which follows, where DBA/2 mice about 20-23 days old are injected intraperitoneally with a test compound 30 minutes prior to being placed in a bell jar with exposure to auditory stimulus of 12KHz sine wave at 110-120 db. References herein *in vivo* "audiogenic 25 assay" are intended to refer to that protocol. Generally preferred compounds exhibit 20% or more inhibition (relative to subjects treated with vehicle control only) at a dose of 20 mg/kg, more preferably about 50% or more inhibition at a dose of 20 mg/kg in such an *in vivo* audiogenic assay. As discussed above, activity in the audiogenic assay has been recognized as 30 indicative that a test compound has neuroprotective properties. See, e.g., M. Tricklbank et al., *European Journal of Pharmacology*, *supra*; T. Seyfried, *Federation Proceedings*, *supra*.

The invention also provides methods for determining binding activity of compounds of the invention as well as *in vitro* and *in vivo* binding activity diagnostic methods using one or more radiolabelled compounds of the invention, e.g., a compound of the invention that is labeled with  $^{125}\text{I}$ , tritium, 5  $^{32}\text{P}$ ,  $^{99}\text{Tc}$ , or the like, preferably  $^{125}\text{I}$ . For instance, a compound of the invention having a phenyl or other aryl substituent that is ring substituted with one or more  $^{125}\text{I}$  groups can be administered to a mammal and the subject then scanned for binding of the compound. Specifically, single photon emission computed tomography ("SPECT") can be employed to detect 10 such binding. Such an analysis of the mammal could e.g. aid in the diagnosis and treatment of acute cerebral ischemia. That is, a labeled compound of the invention will selectively bind to ischemic tissue of e.g. a subject's brain to differentiate between ischemic and non-ischemic tissue and thereby assess trauma or other injury to the brain.

15 Accordingly, the invention includes compounds of the invention that contain a radiolabel such as  $^{125}\text{I}$ , tritium,  $^{32}\text{P}$ ,  $^{99}\text{Tc}$ , or the like, preferably  $^{125}\text{I}$ . Such radiolabelled compounds can be suitably prepared by procedures known in the synthesis art. For example, a compound of the invention 20 having an aromatic group, such as phenyl, that has a bromo or chloro ring substituent can be employed in an exchange labeling reaction to provide the corresponding compound having an  $^{125}\text{I}$  ring substituent.

Compounds of the invention may be used in therapy in conjunction 25 with other medicaments. For example, for treatment of a stroke victim or a person susceptible to stroke, one or more compounds of Formula I may be suitably administered together with a pharmaceutical targeted for interaction in the blood clotting mechanism such as streptokinase, tPA, urokinase and other agents that lyse clots. Also, one or more compounds of 30 the invention may be administered together with agents such as heparin and related heparin-based compounds, acenocoumarol or other known anticoagulants.

- The compounds of this invention can be administered intranasally, orally or by injection, e.g., intramuscular, intraperitoneal, subcutaneous or intravenous injection, or by transdermal, intraocular or enteral means. The optimal dose can be determined by conventional means. Compounds of the invention are suitably administered to a subject in the protonated and water-soluble form, e.g., as a pharmaceutically acceptable salt of an organic or inorganic acid, e.g., hydrochloride, sulfate, hemi-sulfate, phosphate, nitrate, acetate, oxalate, citrate, maleate, mesylate, etc.
- Compounds of the invention can be employed, either alone or in combination with one or more other therapeutic agents as discussed above, as a pharmaceutical composition in mixture with conventional excipient, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral or intranasal application which do not deleteriously react with the active compounds and are not deleterious to the recipient thereof. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are solutions, preferably oily or aqueous solutions as well as suspensions, emulsions, or implants, including suppositories. Ampules are convenient unit dosages.

For enteral application, particularly suitable are tablets, dragees or capsules having talc and/or carbohydrate carrier binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is

employed. Sustained release compositions can be formulated including those wherein the active component is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

5       For topical applications, formulations may be prepared in a topical ointment or cream containing one or more compounds of the invention. When formulated as an ointment, one or more compounds of the invention suitably may be employed with either a paraffinic or a water-miscible base. The one or more compounds also may be formulated with an oil-in-water  
10      cream base. Other suitable topical formulations include e.g. lozenges and dermal patches.

Intravenous or parenteral administration, e.g., sub-cutaneous, intraperitoneal or intramuscular administration are preferred. The  
15      compounds of this invention are particularly valuable in the treatment of mammalian subjects, e.g., humans, to provide neuroprotective therapy and/or prophylaxis. Typically, such subjects include those afflicted with neurodegenerative diseases such as Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Alzheimer's disease, Down's  
20      Syndrome and Korsakoff's disease. Also suitable for treatment are those subjects suffering from or likely to suffer from nervous system dysfunctions resulting from, for example, epilepsy or nerve cell degeneration which is the result of hypoxia, hypoglycemia, brain or spinal chord ischemia or brain or spinal chord trauma. As discussed above, typical candidates for treatment  
25      include heart attack, stroke, brain or spinal cord injury patients, patients undergoing major surgery where brain or spinal cord ischemia is a potential complication and patients such as divers suffering from decompression sickness due to gas emboli in the blood stream.

30       It will be appreciated that the actual preferred amounts of active compounds used in a given therapy will vary according to the specific compound being utilized, the particular compositions formulated, the mode of application, the particular site of administration, etc. Optimal administration rates for a given protocol of administration can be readily

ascertained by those skilled in the art using conventional dosage determination tests conducted with regard to the foregoing guidelines. In general, a suitable effective dose of one or more compounds of the invention, particularly when using the more potent compound(s) of the invention, will  
5 be in the range of from 0.01 to 100 milligrams per kilogram of bodyweight of recipient per day, preferably in the range of from 0.01 to 20 milligrams per kilogram bodyweight of recipient per day, more preferably in the range of 0.05 to 4 milligrams per kilogram bodyweight of recipient per day. The desired dose is suitably administered once daily, or several sub-doses, e.g. 2  
10 to 4 sub-doses, are administered at appropriate intervals through the day, or other appropriate schedule. Such sub-doses may be administered as unit dosage forms, e.g., containing from 0.05 to 10 milligrams of compound(s) of the invention, per unit dosage, preferably from 0.2 to 2 milligrams per unit dosage.

15                   Compounds of the invention also should be useful as rubber accelerators. See U.S. Patent No. 1,411,713 for a discussion of rubber accelerator applications.

20                   The entire text of all documents cited herein are incorporated by reference herein. The following non-limiting examples are illustrative of the invention.

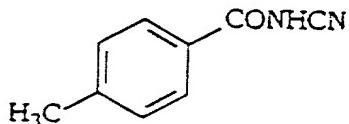
#### GENERAL COMMENTS

25                   Melting points were determined in open capillary tubes on a Mel-Temp II apparatus and are uncorrected. Yields are of isolated products and were not optimized. <sup>1</sup>H-NMR were run on a Varian Gemini 300 MHz spectrophotometer and the chemical shifts were reported in ppm ( $\delta$ ) relative to the residual signal of deuterated solvent ( $\text{CD}_2\text{OD}$  3.30,  $\text{CDCl}_3$  7.26).  
30                   HPLC purity determinations were carried out using a Beckman 126 gradient system with UV detection at 220 nm. Linear 30 minutes gradient:2 to 98%  $\text{CH}_3\text{CN}$  in  $\text{H}_2\text{O}$  (0.1% TFA) Column: Ultrasphere ODS (AC-2) 5mm 4.6 X 250 mm with C-18 guard column, flow rate 1 ml/min.

EXAMPLE 1:      Synthesis of N-(4-methylbenzoyl)-N'-(4-isopropylphenyl)guanidine, hydrochloride (Formula I:  
hydrochloride salt of R=4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; each R<sup>1</sup>=R<sup>2</sup>=H;  
X=chemical bond; R<sup>3</sup>=4-isopropylphenyl)

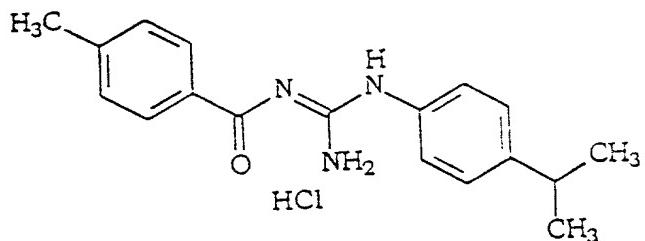
5

Part I:      4-methylbenzoylcyanamide



To a solution of cyanamide (1.05 g, 0.025 mmol) in 25 ml of sodium  
10 hydroxide (10%) was added slowly to a solution of 4-methylbenzoyl chloride  
(3.3 ml, 0.025 mmol) in ether (8 ml). The reaction mixture was stirred at  
room temperature for 1 hour. The reaction mixture then was cooled in ice  
bath and acidified with hydrochloric acid (10%) to pH 2. The white solid  
separated was filtered, washed with water, later hexanes and dried under  
15 high vacuum to give the N-(4-methylbenzoyl)cyanamide (3.4 g); m.p. 140-  
142°C (lit m.p. 149-150°C); purity 88% HPLC; <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ 2.42 (s,  
3H, CH<sub>3</sub>), 7.38 (d, 2H, ArH), 7.78 (d, 2H, ArH).

20 Part II:      N-(4-methylbenzoyl)-N'-(4-isopropylphenyl)guanidine,  
hydrochloride

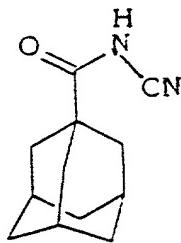


A mixture of N-(4-methylbenzoylcyanamide) (160 mg, 1 mmol) and 4-isopropylaniline•hydrochloride (185 mg [prepared from 4-isopropylaniline

and hydrogen chloride (1M in ether)]) in toluene (4 ml) was refluxed for 3 hours. The reaction mixture was cooled to room temperature, the precipitated white solid was filtered, washed with toluene and finally with hexanes to afford the title product, (268 mg, 78%); m.p. 208-210°C; purity 5 99.3% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  1.28 (2s, 6H,  $\text{CH}_3$ ), 2.42 (s, 3H, Ar- $\text{CH}_3$ ), 3.02 (m, 1H, CH), 7.38 (d, 2H, ArH), 7.42 (m, 4H, ArH), 8.0 (d, 2H, ArH).

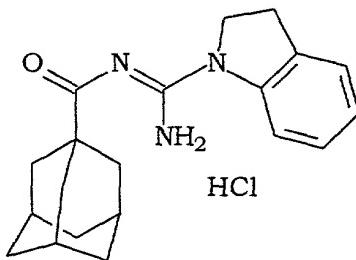
EXAMPLE 2: Preparation of N-(1-adamantancarbonyl)-1-indolinylcarboxamidine, hydrochloride ((Formula II:  
10 hydrochloride salt of R=1-adamantyl; each  $\text{R}^1=\text{R}^2=\text{R}^3=\text{H}$ )

Part I: Adamantancarbonylcyanamide



15 To a solution of cyanamide (2.52 g, 0.06 mol) in 24 ml of sodium hydroxide (10%) was added slowly to a solution of 1-adamantancarbonylchloride (4g, 0.02 mol) in ether (15 ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with ether and the aqueous layer was cooled in ice bath and  
20 acidified with hydrochloric acid (10%) to pH 2. The precipitated white solid was filtered, washed with water, later hexanes and dried under high vacuum to give the N-(1-adamantancarbonyl)cyanamide (3.2 g, 78%); m.p. 164-166°C (lit m.p. 168-170°C); purity 94% HPLC;  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  1.45-2.16 (m, 15H,  $\text{CH}_2$  and CH).

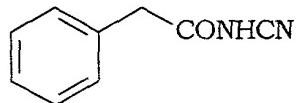
25 Part II: N-(1-adamantancarbonyl)-1-indolinylcarboxamidine,  
hydrochloride



A mixture of N-(1-adamantanecarbonyl)cyanamide (200 mg, 0.88 mmol) and indoline hydrochloride (155 mg [prepared from indoline and hydrogen chloride (1M in ether)]) in toluene (4 ml) was refluxed for 3 hours. The reaction mixture was cooled to room temperature, the precipitated white solid was filtered, washed with toluene and finally with hexanes to afford the title product, (339 mg, 78%); m.p. 252-256°C; Purity 99% (HPLC); <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ 1.65 (m, 15H, CH<sub>2</sub> and CH), 3.2 (t, 2H, ArCH<sub>2</sub>), 4.2 (t, 2H, NCH<sub>2</sub>), 7.25 (m, 1H, arH), 7.36 (m, 2H, ArH), 7.42 (m, 1H, ArH).

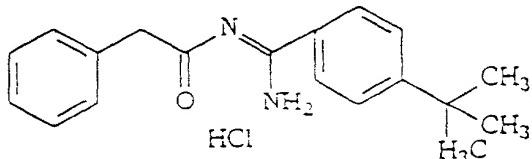
EXAMPLE 3: Preparation of N-(phenylacetyl)-N'-(4-t-butylphenyl)guanidine, hydrochloride (Formula I: hydrochloride salt of R=C<sub>6</sub>H<sub>5</sub>; each R<sup>1</sup>=R<sup>2</sup>=H; X=chemical bond; R<sup>3</sup>=4-tert-butylphenyl)

Part I: Phenylacetylcyanamide



This compound was prepared in 83% yield by the method described in Example 2, Part I above using phenylacetyl chloride in place of adamantan-1-carbonyl chloride. Phenylacetylcyanamide: a white solid; purity 92% (HPLC); <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ 2.3 (s, 2H), 7.25-7.45 (m, 5H).

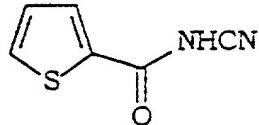
Part II: N-(Phenylacetyl)-N'-(4-t-butylphenyl)guanidine, hydrochloride



Synthesis of this compound was achieved by the method set forth in Example 1, Part II above with the use of phenylacetylcyanamide in place of 4-methylbenzoylcyanamide and using 4-t-butylaniline hydrochloride instead of 4-isopropylaniline hydrochloride respectively. Yield 69%; m.p. 182-186°C; Purity 86% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  1.38 (s, 9H,  $\text{CH}_3$ ), 3.84 (s, 2H,  $\text{CH}_2$ ), 7.3 (d, 2H, ArH), 7.3-7.45 (m, 5H, ArH), 7.6 (d, 2H, ArH).

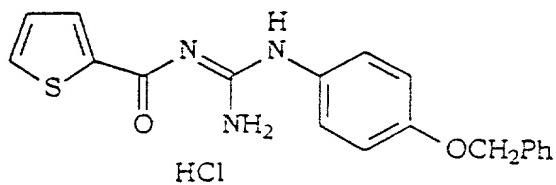
10 EXAMPLE 4: Preparation of N-(2-thiophenecarbonyl)-N'-(4-benzyloxyphenyl)guanidine, hydrochloride (Formula I: hydrochloride salt of R=2-thiophenyl; each  $\text{R}^1=\text{R}^2=\text{H}$ ; X=chemical bond;  $\text{R}^3=4-\text{C}_6\text{H}_5\text{CH}_2\text{OC}_6\text{H}_4-$ )

15 Part I: (2-Thiophenecarbonyl)cyanamide



This compound was prepared in 73% yield by the method described in Example 2, Part I above using 2-thiophenecarbonylchloride in place of adamantine-1-carbonyl chloride. N-(2-thiophenecarbonyl)cyanamide: a white solid; purity 96% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  7.2 (m, 1H), 7.8 (d, 1H), 7.9 (d, 1H).

25 Part II: N-(2-Thiophenecarbonyl)-N'-(4-benzyloxyphenyl)guanidine, hydrochloride

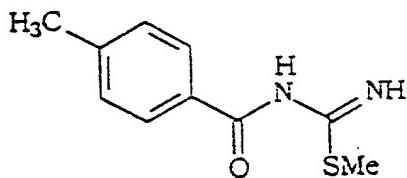


Synthesis of this compound was achieved by the method set forth in Example 1, Part II above with the use of N-(2-thiophenecarbonyl)cyanamide

in place of N-(4-methylbenzoylcyanamide) and using 4-benzylcyanamide and using 4-benzyloxyaniline hydrochloride instead of 4-isopropylaniline hydrochloride respectively. Yield 61%; m.p. 198-202°C; Purity 93% (HPLC);  
1 H-NMR (CD<sub>3</sub>OD) δ 5.18 (s, 2H, CH<sub>2</sub>), 7.18 (d, 2H), 7.22-7.4 (m, 6H), 7.44 (d, 5 H), 7.9 (d, 1H), 8.18 (d, 1H).

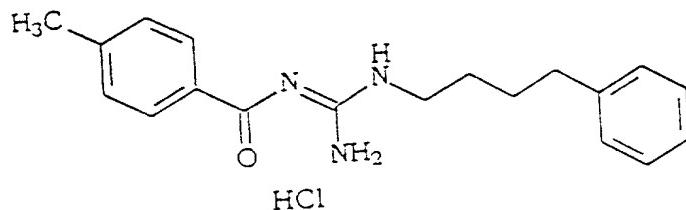
EXAMPLE 5 : Preparation of N-(4-methylbenzoyl)-N'-(4-phenylbutyl)guanidine, hydrochloride (Formula I:  
10 hydrochloride salt of R=4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; each R<sup>1</sup>=R<sup>2</sup>=H;  
X=CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>; R<sup>3</sup>=C<sub>6</sub>H<sub>5</sub>)

Part I: N-(4-Methylbenzoyl)-S-methylisothiourea



15 A solution of 2-methyl-2-thiopseudourea sulfate (6.9 g, 0.025 mol) in  
30 ml of sodium hydroxide (4%) was added a solution of 4-methylbenzoyl  
chloride (3.4 g, 0.022 mol) in ether (10 ml) at room temperature. The  
reaction mixture was stirred overnight and the precipitated solid was  
filtered, washed with water, later hexanes and dried under high vacuum. N-  
20 (4-methylbenzoyl)-S-methylisothiourea: yield 4.60 g (quantitative); purity  
98% (HPLC); <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ 2.4 (s, 3H, CH<sub>3</sub>), 2.6 (s, 3H, SMe), 7.2 (d,  
2H, ArH), 8.1 (d, 2H, ArH).

25 Part II: N-(4-methylbenzoyl)-N'-(4-phenylbutyl)guanidine,  
hydrochloride

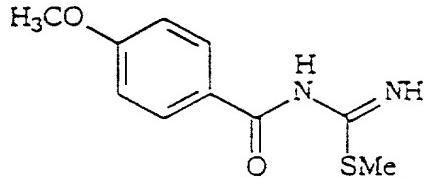


Phenylbutyl amine (0.75 ml, 4.75 mmol) and triethylamine (0.7 ml, 5 mmol) was added to a suspension of the thiourea derivative (1.04 g, 5 mmol), prepared in Part I, in toluene (10 ml). The reaction mixture was  
5 heated in an oilbath to reflux and maintained at reflux for 3 hours. The free base separated on cooling was filtered, washed with hexanes and dried to afford the solid (1.3 g).

The free base (1.3 g) was dissolved in methanol (30 ml) and  
10 dichloromethane (25 ml) and cooled in an ice water bath. Hydrogen chloride (1M in ether, 20 ml) was added, stirred for 30 minutes, concentrated under reduced pressure. N-(4-methylbenzoyl)-N'-(4-phenylbutyl)guanidine, hydrochloride: white solid (1.43 g, 84%); m.p. 166-170°C; Purity: 99% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  1.74 (m, 4H,  $\text{CH}_2$ ), 2.43 (s, 3H,  $\text{CH}_3$ ), 2.69 (t, 2H,  $\text{CH}_2$ ), 3.38 (t, 2H,  $\text{CH}_2$ ), 7.2 (m, 5H, ArH), 7.4 (d, 2H, ArH), 7.9 (d, 2H, ArH).  
15

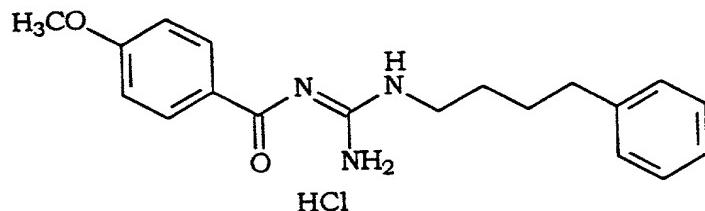
EXAMPLE 6: Preparation of N-(4-methoxybenzoyl)-N'-(4-phenylbutyl)guanidine, hydrochloride (Formula I: hydrochloride salt of R=4- $\text{CH}_3\text{OC}_6\text{H}_4$ ; each  $\text{R}^1=\text{R}^2=\text{H}$ ; X= $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ;  $\text{R}^3=\text{C}_6\text{H}_5$ )  
20

Part I: N-(4-Methoxybenzoyl)-S-methylisothiourea



Synthesis of this compound was achieved by the method set forth in Example 5, Part I above with the use of 4-methoxybenzoyl chloride in place of 4-methylbenzoyl chloride. N-(4-methoxybenzoyl)-S-methylisothiourea: white solid (83% yield); Purity 99% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  2.57 (s, 3H,  $\text{SCH}_3$ ), 3.86 (s, 3H,  $\text{OCH}_3$ ), 6.94 (d, 2H, ArH), 8.15 (d, 2H, ArH).  
25

Part II: N-(4-Methoxybenzoyl)-N'-(4-phenylbutyl)guanidine,  
hydrochloride



5

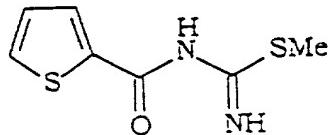
Preparation of this compound was carried out by the method as described in Example 5, Part II above using 4-methoxybenzoyl-S-methylisothiourea in place of 4-methylbenzoyl-S-methylisothiourea. N-(4-methoxybenzoyl)-N'-(4-phenylbutyl)guanidine, hydrochloride: white solid (55%); m.p. 172-174°C; Purity 99% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  1.74 (m, 4H,  $\text{CH}_2$ ), 2.67 (t, 2H,  $\text{CH}_2$ ), 3.37 (t, 2H,  $\text{CH}_2$ ), 3.89 (s, 3H,  $\text{OCH}_3$ ), 7.10 (d, 2H, ArH), 7.22 (m, 5H, ArH), 7.97 (d, 2H, ArH).

10

EXAMPLE 7: N-(2-thiophenecarbonyl)-N'-(2-phenylethyl)guanidine,  
hydrochloride (Formula I: hydrochloride salt of R=2-thiophenyl; each  $\text{R}^1=\text{R}^2=\text{H}$ ;  $\text{X}=\text{CH}_2\text{CH}_2$ ;  $\text{R}^3=\text{C}_6\text{H}_5$ )

15

Part I: N-(2-Thiophenecarbonyl)-S-methylisothiourea

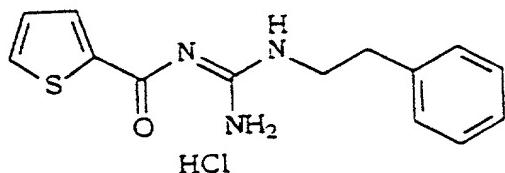


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Synthesis of this compound was achieved by the method set forth in Example 5, Part I above with the use of 2-thiophenecarbonyl chloride in place of 4-methylbenzoyl chloride. N-(2-thiophenecarbonyl)-S-methylisothiourea: white solid (73% yield); Purity 91.2% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  2.76 (s, 3H,  $\text{SCH}_3$ ), 7.26 (m, 1H, ArH), 8.01 (d, 1H, ArH), 8.12 (d, 1H, ArH).

25

Part II: N-(2-Thiophenecarbonyl)-N'-(2-phenylethyl)guanidine,  
hydrochloride

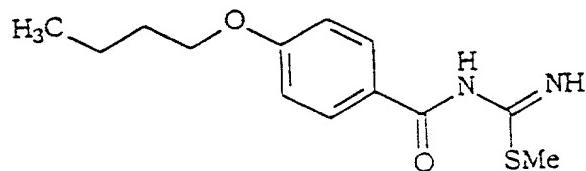


5

Preparation of this compound was carried out by the method as described in Example 5, Part II above using N-(2-thiophenecarbonyl)-S-methylisothiourea in place of 4-methylbenzoyl-S-methylisothiourea and 2-phenylethylamine instead of 4-phenylbutylamine respectively. N-(2-thiophenecarbonyl)-N'-(2-phenylethyl)guanidine, hydrochloride: white solid (58%); m.p. 198-200°C; Purity 97% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  3.00 (t, 2H,  $\text{CH}_2$ ), 3.65 (t, 2H,  $\text{CH}_2$ ), 7.2 (d, 1H, ArH), 7.28 (m, 5H, ArH), 7.97 (d, 2H, ArH).

15 EXAMPLE 8: N-(4-Butoxybenzoyl)-N'-[2-(indol-3-yl)ethyl]guanidine,  
hydrochloride (Formula I: hydrochloride salt of R=4-  
 $\text{CH}_3(\text{CH}_2)_3\text{OC}_6\text{H}_4$ ; each  $\text{R}^1=\text{R}^2=\text{H}$ ; X= $\text{CH}_2\text{CH}_2$ ;  $\text{R}^3=3$ -  
indol)

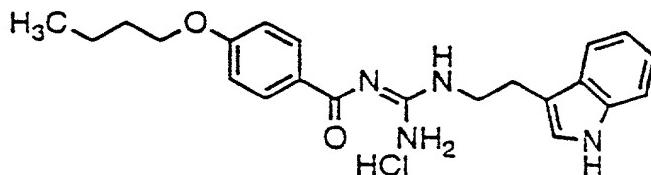
20 Part I: N-(4-Butoxybenzoyl)-S-methylisothiourea



25 This compound was prepared following the method as described in Example 6, Part I above using 4-butoxybenzoyl chloride in place of 4-methoxybenzoyl chloride. N-(4-butoxybenzoyl)-S-methylisothiourea: white solid (85%); Purity 95% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  1.0 (t, 3H,  $\text{CH}_3$ ), 1.50 (m,

2H, CH<sub>2</sub>), 1.78 (m, 2H, CH<sub>2</sub>), 2.56 (s, 3H, SCH<sub>3</sub>), 4.03 (t, 2H, OCH<sub>2</sub>), 6.93 (d, 2H, ArH), 8.14 (d, 2H, ArH).

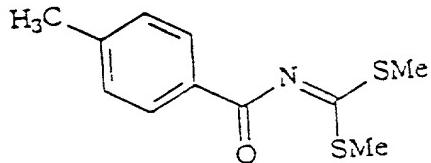
Part II: N-(4-Butoxybenzoyl)-N'-[2-(indol-3-yl)ethyl]guanidine,  
5 hydrochloride



Preparation of this compound was carried out by the method as described in Example 5, Part II above using N-(4-butoxybenzoyl)-S-methylisothiourea in place of 4-methylbenzoyl-S-methylisothiourea and 3-(2-aminoethyl)indole (tryptamine) instead of 4-phenylbutylamine respectively. N-(4-butoxybenzoyl)-N'-[2-(indol-3-yl)ethyl]guanidine, hydrochloride: solid (yield 28%); m.p. 158-162°C; Purity 95% (HPLC); <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ 0.99 (t, 3H, CH<sub>3</sub>), 1.49 (m, 2H, CH<sub>2</sub>), 1.76 (m, 2H, CH<sub>2</sub>), 3.28 (t, 2H, CH<sub>2</sub>), 3.69 (t, 2H, CH<sub>2</sub>), 4.05 (t, 2H, CH<sub>2</sub>), 7.04 (m, 4H, ArH), 7.2 (d, 1H), 7.32 (d, 1H, ArH), 7.56 (d, 1H, ArH), 7.86 (d, 2H, ArH).

EXAMPLE 9: N-(4-Methylbenzoyl)-N'-(4-phenylbutyl)-N"-methylguanidine, hydrochloride (Formula I: hydrochloride salt of R=4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; first R<sup>1</sup>=CH<sub>3</sub>, second R<sup>1</sup>=H; R<sup>2</sup>=H; X=CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>; R<sup>3</sup>=C<sub>6</sub>H<sub>5</sub>)  
20

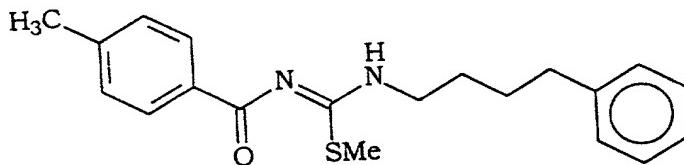
Part I: Dimethyl N-(4-methylbenzoylcarbimidodithiolate)



A mixture of 4-methylbenzamide (1.35 g, 0.01 mol) in anhydrous tetrahydrofuran (50 ml), carbon disulfide (3 g, 0.039 mol), and methyl iodide (4.5 g, 0.032 mol), and sodium hydride (0.85 g, 60% dispersion in oil, 0.02 mol) was stirred at room temperature overnight. The reaction mixture was 5 poured onto ice, extracted with ethyl acetate (3 X 30 ml), washed with water, dried and concentrated to give an oil. This solidified on standing and was crystallized from hexanes as bright yellow crystals (0.8 g); m.p. 57-59°C (lit 60-61°C); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.40 (s, 3H, Ar-Me), 2.57 (s, 6H, SMe), 7.25 (d, 2H, ArH), 7.98 (d, 2H, ArH).

10

Part II: N-(4-methylbenzoyl)-N'-(4-phenylbutyl)-S-Methylthiourea

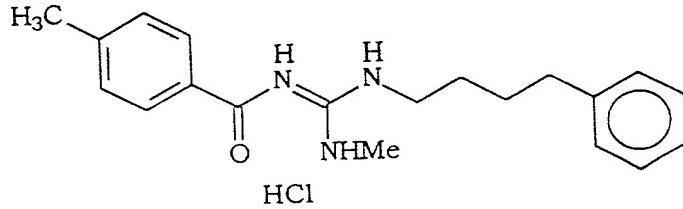


15

A mixture of dimethyldithiolate (240 mg, mmol, prepared as in Part I) and phenylbutylamine (150 mg, mmol) in ethanol (5 ml) was stirred overnight at room temperature. The reaction mixture was concentrated and the oil obtained was repeatedly coevaporated with dichloromethane, upon which solid separated. This solid was triturated with hexanes, filtered and dried. N-(4-methylbenzoyl)-N'-(4-phenylbutyl)-S-Methylthiourea: white 20 solid (80 mg); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.85 (m, 4H, CH<sub>2</sub>), 2.38 (s, 3H, ArMe), 2.61 (s and t, 5H, CH<sub>2</sub> and Sme), 3.35 (t, 2H, CH<sub>2</sub>), 7.2 (m, 5H, ArH), 7.28 (d, 2H, ArH), 8.12 (d, 2H, ArH).

25

Part III: N-(4-Methylbenzoyl)-N'-(4-phenylbutyl)-N"-methylguanidine, hydrochloride



A solution of N-(4-methylbenzoyl)-N'-(4-phenylbutyl)-S-Methylthiourea (80 mg, prepared as in Part II) in 5 ml of methylamine (2M in methanol) was stirred at room temperature for 48 hours. After removal of the solvent the residue was dissolved in methanol (3 ml), and a ethereal  
5 solution of hydrogen chloride (5 ml) was added. The solid separated was filtered, washed with ether and dried. Pale yellow solid (50 mg); Purity: 93% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  1.71 (m, 4H,  $\text{CH}_2$ ), 2.40 (s, 3H,  $\text{ArCH}_3$ ), 2.65 (t, 2H,  $\text{CH}_2$ ), 3.05 (s, 3H,  $\text{NMe}$ ), 3.4 (t, 2H,  $\text{CH}_2$ ), 7.13 (m, 5H, Ar), 7.35 (d, 2H, ArH), 7.82 (d, 2H, ArH).

10

EXAMPLE 10: N-(2,6-Dichlorophenylacetyl)-N'-benzylguanidine hydrochloride (Formula I': hydrochloride salt of R=2,6-di- $\text{C}_6\text{H}_3$ ; both  $\text{R}^1=\text{H}$ ;  $\text{R}^2=\text{H}$ ; X= $\text{CH}_2$ ;  $\text{R}^3=\text{C}_6\text{H}_5$ )

15

Part I: Benzylguanidine hydrochloride

A mixture of benzylamine hydrochloride (4.3g, 0.03 mol) and cyanamide (1.3g, 0.031 mol) in xylenes (15 ml) was heated to reflux for 6 hours. After concentration, the reaction mixture was triturated with ether and the solid separated was filtered and crystallized from methanol to  
20 provide a colorless solid (2.38 g); purity: 96.8% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  4.41 (s, 2H,  $\text{CH}_2$ ), 7.32-7.37 (m, 5H, Ar).

Part II: N-(2,6-Dichlorophenylacetyl)-N'-benzylguanidine hydrochloride  
To sodium ethoxide [prepared by reacting sodium (60 mg, 2.61 mmol)  
25 and anhydrous ethanol (5 ml)] benzylguanidine hydrochloride (580 mg, 3.12 mmol) was added and refluxed in an oilbath for 1 hour. The reaction mixture was cooled to room temperature and insoluble materials filtered. Methyl 2,6-dichlorophenylacetate (285 mg, 1.3 mmol) ( $\text{CH}_3(\text{C=O})\text{CH}_2(2,6,\text{-di-ClC}_6\text{H}_3)$  was added to the filtrate and refluxed for 2 hours. After cooling to  
30 room temperature the reaction mixture was concentrated and converted to the hydrochloride salt by the addition of hydrogen chloride (1M in ether) to provide 310 mg of N-(2,6-dichlorophenylacetyl)-N'-benzylguanidine

hydrochloride as a white solid, purity 89.3% (HPLC);  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  4.38 (s, 4H,  $\text{CH}_2$ ), 7.32-7.41 (m, 8H, Ar).

EXAMPLE 11      In vivo Anticonvulsant activity in the DBA/2 mouse  
5                    model (Mouse audiogenic assay)

The in vivo potency of compounds of the invention is exemplified by data summarized in the Table I below and obtained pursuant to the following protocol.

10                Compounds were tested for their effectiveness in preventing seizures in DBA/2 mice which have a unique sensitivity to auditory stimulation. Exposure to loud high-frequency sounds can trigger seizure activity in these animals. This sensitivity develops from postnatal day 12 and peaks around day 21 and slowly diminishes as the animals mature. The unusual  
15                response to auditory stimulation in this strain of mouse is believed to be due to a combination of early myelination (causing an unusually low excitatory threshold) and delayed development of inhibitory mechanisms.

20                Mice were injected intraperitoneally with the compound specified in Table I below or with vehicle control, 30 minutes prior to being placed in a bell jar and turning on the auditory stimulus (12 KHz sine wave at 110-120 db). Administered doses are specified in Table I as milligram of compound per kilogram bodyweight of mouse. The auditory stimulus was left on for 60 seconds and mice reactions were timed and recorded. Percentage inhibition  
25                was determined with reference to vehicle controls. Results are shown in the Table I below. All compounds were tested in HCl salt form.

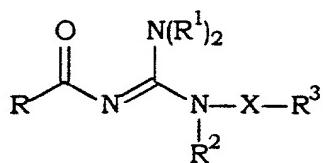
Table I

Compound Name	Audiogenic Response	
	Dose (mg/kg)	% Inhib.
N-(4-methylbenzoyl)-N'-(4-isopropylphenyl)guanidine	20	30
N-(4-methylbenzoyl)-N'-(4-phenylbutyl)guanidine	20	75
	10	16
N-(4-methoxybenzoyl)-N'-(4-phenylbutyl)guanidine	20	42
N-(4-methoxyphenyl)-N'-(4-isopropylphenyl)guanidine	20	56
N-(4-ethoxyphenyl)-N'-(4-phenylbutyl)guanidine	20	60
N-(4-butoxyphenyl)-N'-(4-phenylbutyl)guanidine	20	97

This invention has been described in detail with reference to  
5 preferred embodiments thereof. However, it will be appreciated that those  
skilled in the art, upon consideration of this disclosure, may make  
modifications and improvements within the spirit and scope of the  
invention.

What is claimed is:

1. A compound of the following Formula:



wherein R is an optionally substituted cyclic alkyl; an optionally substituted carbocyclic aryl; an optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; optionally substituted aralkyl; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl;

each R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted or unsubstituted carbocyclic aryl; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and 1 to about 3 hetero atoms;

X is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene; and

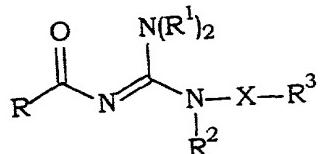
R<sup>3</sup> is an optionally substituted cyclic alkyl; optionally substituted carbocyclic aryl, optionally substituted alkylaryl; or optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; and pharmaceutically acceptable salts thereof.

2. A compound of claim 1 having the following Formula:



wherein  $\text{R}$ ,  $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  are each the same as defined in claim 1; and pharmaceutically acceptable salts of said compounds.

3. A compound of claim 1 having the following Formula:



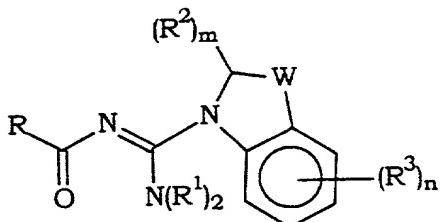
wherein  $\text{X}$  is an alkylene linkage;  $\text{R}$ ,  $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  are each the same as defined in claim 1; and pharmaceutically acceptable salts of those compounds.

4. A compound of any one of claims 1-3 wherein  $\text{R}^2$  is hydrogen.

5. A compound of any one of claims 1-3 wherein  $\text{R}^2$  is optionally substituted alkyl.

6. A compound of any one of claims 1-3 wherein  $\text{R}^2$  is  $\text{C}_{1-3}$  alkyl.

7. A compound of the following Formula:



wherein R is an optionally substituted cyclic alkyl; an optionally substituted carbocyclic aryl; an optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; optionally substituted aralkyl; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl;

each R¹ is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted or unsubstituted carbocyclic aryl; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and 1 to about 3 hetero atoms;

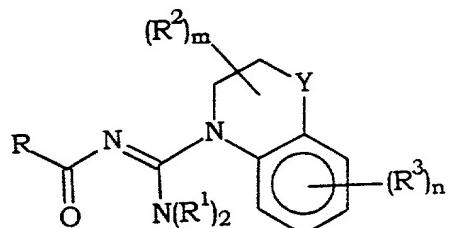
each R² and each R³ are independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted aminoalkyl, optionally substituted carbocyclic aryl, or optionally substituted aralkyl;

W is optionally substituted methylene, -S-, -O-, optionally substituted -N-, -S(O)- or -S(O₂)-;

m is 0, 1 or 2; n is 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

8. A compound of claim 7 wherein W is optionally substituted methylene.

9. A compound of the following Formula:



wherein R is an optionally substituted cyclic alkyl; optionally substituted carbocyclic aryl; optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; optionally substituted aralkyl; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl;

each R<sup>1</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted or unsubstituted carbocyclic aryl; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and 1 to about 3 hetero atoms;

each R<sup>2</sup> and each R<sup>3</sup> are independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted aminoalkyl, optionally substituted carbocyclic aryl, or optionally substituted aralkyl;

Y is optionally substituted methylene, -O-, -S-, -S(O)-, -S(O<sub>2</sub>)-, or optionally substituted -N-,

m and n are each independently 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

10. A compound of claim 1, 7 or 9 that is:

N-(4-methylbenzoyl)- N'-methyl-N'-(3-methylthiophenyl)guanidine;  
N-(4-methylbenzoyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(4-methylbenzoyl)-N'-(1-naphthyl)guanidine;  
N-(4-methylbenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(4-methylbenzoyl)-N'-(4-tertbutylphenyl)guanidine;  
N-(4-methylbenzoyl)-1-indolinylcarboximidamide;  
N-(4-methylbenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(4-methylbenzoyl)-1-[7-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline] carboximidamide;  
N-(4-methylbenzoyl)-1-(1,2,3,4-tetrahydroquinoline)carboximidamide;  
N-(4-methylbenzoyl)-N'-(2,5-dibromophenyl)guanidine;  
N-(4-methylbenzoyl)-N'-(4-isopropoxyphenyl)guanidine;  
N-(4-methylbenzoyl)-N'-(3,4,5-trimethoxyphenyl)guanidine;  
N-(4-methylbenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(2,5-dichlorobenzoyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(2,5-dichlorobenzoyl)- N'-methyl-N'-(3-methylthiophenyl)guanidine;  
N-(2,5-dichlorobenzoyl)-N'-(1-naphthyl)guanidine;  
N-(2,5-dichlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(2,5-dichlorobenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(2,5-dichlorobenzoyl)-N'-(4-tertbutylphenyl)guanidine;  
N-(2,5-dichlorobenzoyl)-1-indolinylcarboximidamide;  
N-(2,5-dichlorobenzoyl)- N'-methyl-N'-(4-isopropylphenyl)guanidine;  
N-(phenylacetyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(phenylacetyl)-N'-(4-isopropylphenyl)guanidine;  
N-(phenylacetyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(phenylacetyl)-1-indolinylcarboximidamide;  
N-(phenylacetyl)-1-(1,2,3,4-tetrahydroquinoline)carboximidamide;  
N-(phenylacetyl)-N'-(4-isopropoxyphenyl)guanidine;  
N-(phenylacetyl)-N'-(4-isopropylphenyl)-N'-methylguanidine;  
N-(adamantan-1-carbonyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(adamantan-1-carbonyl)-N'-(1-naphthyl)guanidine;  
N-(adamantan-1-carbonyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(adamantan-1-carbonyl)-N'-(4-isopropylphenyl)guanidine;

N-(adamantan-1-carbonyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(adamantan-1-carbonyl)-1-(indolinyl)carboximidamide;  
N-(adamantan-1-carbonyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(adamantan-1-carbonyl)-N'-(2,5-dibromophenyl)guanidine;  
N-(adamantan-1-carbonyl)-N'-(4-isopropylphenyl)-N'-methyl)guanidine;  
N-(4-chlorobenzoyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(4-chlorobenzoyl)-N'-methyl-N'-(3-methylthiophenyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(1-naphthyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(4-chlorobenzoyl)-1-(indolinyl)carboximidamide;  
N-(4-chlorobenzoyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(4-chlorobenzoyl)-N'-(2,5-dibromophenyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(1-naphthyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(3,4-dichlorobenzoyl)-1-(indolinyl)carboximidamide;  
N-(3,4-dichlorobenzoyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(3,4-dichlorobenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-methyl-N'-(3-methylthiophenyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(1-naphthyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(4-isopropylphenyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(thiophen-2-carbonyl)-1-(indolinyl)carboximidamide;  
N-(thiophen-2-carbonyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(thiophen-2-carbonyl)-N'-(4-isopropylphenyl)guanidine;  
N-(furan-2-carbonyl)-N'-methyl-N'-(3-iodophenyl)guanidine;  
N-(furan-2-carbonyl)-N'-methyl-N'-(3-methylthiophenyl)guanidine;  
N-(furan-2-carbonyl)-N'-(1-naphthyl)guanidine;

N-(furan-2-carbonyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(furan-2-carbonyl)-N'-(4-isopropylphenyl)guanidine;  
N-(furan-2-carbonyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(furan-2-carbonyl)-1-(indolinyl)carboximidamide;  
N-(furan-2-carbonyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(furan-2-carbonyl)-N'-(4-isopropylphenyl)-N'-methylguanidine;  
N-(pyridin-3-carbonyl)-N'-(1-naphthyl)guanidine;  
N-(pyridin-3-carbonyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(pyridin-3-carbonyl)-N'-(4-isopropylphenyl)guanidine;  
N-(pyridin-3-carbonyl)-N'-(4-tert-butylphenyl)guanidine;  
N-(pyridin-3-carbonyl)-1-(indolinyl)carboximidamide;  
N-(pyridin-3-carbonyl)-1-(1,2,3,4-tetrahydroquinolinyl)carboximidamide;  
N-(4-methoxybenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(4-isopropoxypyhenyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(3,4,5-trimethoxyphenyl)guanidine;  
N-(1-naphthoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(1-naphthoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(1-naphthoyl)-N'-(4-isopropoxypyhenyl)guanidine;  
N-(3,4,5-trimethoxybenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(3,4,5-trimethoxybenzoyl)-N'-(4-isopropoxypyhenyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(4-isopropoxypyhenyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(3,4,5-trimethoxyphenyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(4-isopropoxypyhenyl)guanidine;  
N-(4-methylbenzoyl)-N'-(benzyl)guanidine;  
N-(4-methylbenzoyl)-N'-(2-phenethyl)guanidine;  
N-(4-methylbenzoyl)-N'-(3-dimethylaminopropyl)guanidine;  
N-(4-methylbenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-methylbenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-methylbenzoyl)-N'-(1-naphthylmethyl)guanidine;  
N-(4-methylbenzoyl)-N'-(2-(4-chlorophenyl)ethyl)guanidine;  
N-(4-methylbenzoyl)-N'-(5-phenylpentyl)guanidine;

N-(4-methylbenzoyl)-N'-(3-phenoxypropyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(benzyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(benzyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(2-phenethyl)guanidine;  
N-(4-chlorobenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(benzyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(3-dimethylaminopropyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(2-phenethyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(2-(4-chlorophenylethyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(1-naphthylmethyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(3,4,5-trimethoxybenzyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(2-phenethyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(2-(4-chlorophenyl)ethyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(1-naphthylmethyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(2-phenethyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(2-(4-chlorophenyl)ethyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(2-(3-indole)ethyl)guanidine;  
N-(3,4,5-trimethoxybenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(3,4,5-trimethoxybenzoyl)-N'-(2-(3-indole)ethyl)guanidine;  
N-(3,4,5-trimethoxybenzoyl)-N'-(2-phenylethyl)guanidine;  
N-(1-naphthoyl)-N'-(benzyl)guanidine;  
N-(1-naphthoyl)-N'-(3-dimethylaminopropyl)guanidine;  
N-(1-naphthoyl)-N'-(2-phenylethyl)guanidine;  
N-(1-naphthoyl)-N'-(4-phenylbutyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(benzyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(3-dimethylaminopropyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(2-phenylethyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(4-phenylbutyl)guanidine;

N-(4-methylbenzoyl)-N'-(cyclohexyl)-N''-methylguanidine;  
N-(4-methylbenzoyl)-N'-(4-phenylbutyl)-N''-methylguanidine;  
N-(4-methoxybenzoyl)-N'-(5-phenylpentyl)guanidine;  
N-(2-methylbenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(2-methylbenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(2-methylbenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(2-methylbenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(2-phenoxypropyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(5-phenylpentyl)guanidine;  
N-(4-methylbenzoyl)-N'-(2-phenoxyethyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(2-phenoxyethyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(2-benzylthio)ethyl]guanidine;  
N-(4-ethoxybenzoyl)-N'-(3,4,5-trimethoxyphenyl)guanidine;  
or a pharmaceutically acceptable salt of any of said compounds.

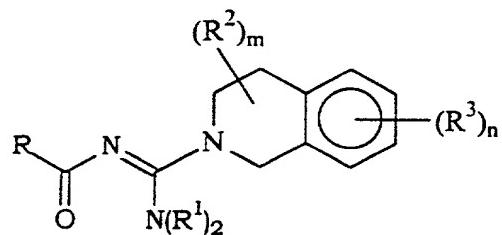
11. A compound of any of claims 1, 7 or 9 that is:

N-(2-methylbenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(2-methylbenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(3,4,5-trimethoxyphenyl)guanidine;  
N-benzoyl-N'-(4-isopropylphenyl)guanidine;  
N-benzoyl-N'-(4-isopropoxyphenyl)guanidine;  
N-benzoyl-N'-(4-benzyloxyphenyl)guanidine;  
N-benzoyl-N'-(2-isopropylphenyl)guanidine;  
N-(2,6-dichlorophenacetyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(2,6-dichlorophenacetyl)-N'-(phenyl)guanidine;  
N-(2,6-dichlorophenacetyl)-N'-(4-isopropyl)phenylguanidine;  
N-(2,6-dichlorophenacetyl)-1-(indolinyl)carboxamidamide;  
N-(2-chlorobenzoyl)-N'-(4-isopropyl)phenylguanidine;  
N-(2-chlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(2-chlorobenzoyl)-1-(indolinyl)carboxamidamide;  
N-(2,6-dichlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(2,6-dichlorobenzoyl)-N'-(2-isopropylphenyl)guanidine;  
N-(2,6-dichlorobenzoyl)-N'-(4-isopropylphenyl)guanidine;  
N-(2,6-dichlorobenzoyl)-1-(indolinyl)carboxamidamide;

N-(2,6-dichlorobenzoyl)-N'-(trimethoxyphenyl)guanidine;  
N-(2,3-dichlorobenzoyl)-N'-(4-isopropyl)phenylguanidine;  
N-(2,3-dichlorobenzoyl)- 1-(indolinyl)carboxamidamide;  
N-(2,3-dichlorobenzoyl)-N'-(4-benzyloxyphenyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(5-phenylpentyl)guanidine;  
N-(2-methylbenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(2-methylbenzoyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(3-phenoxypropyl)guanidine;  
N-(4-butoxybenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(4-methoxybenzoyl)-N'-(3-phenoxyethyl)guanidine;  
N-(4-ethoxybenzoyl)-N'-(3-benzylthioethyl)guanidine;  
N-benzoyl-N'-(4-phenylbutyl)guanidine;  
N-benzoyl-N'-(3-phenoxypropyl)guanidine;  
N-benzoyl-N'-(3,4,5-trimethoxybenzyl)guanidine;  
N-benzoyl-N'-(2-benzylthioethyl)guanidine;  
N-(4-methylbenzoyl)-N'-[[(indol-3-yl)-2-ethyl]guanidine;  
N-(4-chlorobenzoyl)-N'-[[(indol-3-yl)-2-ethyl]guanidine;  
N-(1-naphthoyl)-N'-[[(indol-3-yl)-2-ethyl]guanidine;  
N-(thiophen-2-carbonyl)-N'-[[(indol-3-yl)-2-ethyl]guanidine;  
N-(4-methylbenzoyl)-N'-butylguanidine;  
N-(furan-2-carbonyl)-N'-(3-phenylpropyl)guanidine;  
N-(4-methylbenzoyl)-N'-(2-benzylthioethyl)guanidine;  
N-(4-methylbenzoyl)-N'-(1-indanyl)guanidine;  
N-(N-(4-chlorobenzoyl)-N'-(1-indanyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(1-indanyl)guanidine;  
N-(1-naphthoyl)-N'-[[(imidazol-1-yl)-3-propyl]guanidine;  
N-(furan-2-carbonyl)-N'-[[(imidazol-1-yl)-3-propyl]guanidine;  
N-(4-chlorobenzoyl)-N'-(2-benzylthioethyl)guanidine;  
N-(3,4-dichlorobenzoyl)-N'-(2-benzylthioethyl)guanidine;  
N-(1-naphthoyl)-N'-(2-benzylthioethyl)guanidine;  
N-(thiophen-2-carbonyl)-N'-(2-benzylthioethyl)guanidine;  
N-(4-methylbenzoyl)-N'-[[(thiophen-2-yl)-2-ethyl]guanidine;  
N-(3,4-dichlorobenzoyl)-N'-[[(thiophen-2-yl)-2-ethyl]guanidine;  
N-(3,4,5-trimethoxybenzoyl)-N'-[[(thiophen-2-yl)-2-ethyl]guanidine;

N-(furan-2-carbonyl)-N'-(thiophen-2-yl)-2-ethyl]guanidine;  
N-(thiophen-2-carbonyl)-N'-(thiophen-2-yl)-2-ethyl]guanidine;  
N-(2,3-dichlorobenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(2,5-dichlorobenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(2,6-dichlorobenzoyl)-N'-(4-phenylbutyl)guanidine;  
N-(2,6-dichlorophenylacetyl)-N'-benzylguanidine;  
N-(4-methylbenzoyl)-N'-(2-phenoxyethyl)guanidine;  
N-(benzoyl)-N'-(indol-3-yl-2-yl)guanidine;  
N-(1-naphthoyl)-N'-(4-chlorobenzyl)guanidine; or  
N-(3,4-dichlorobenzoyl)-N'-(imidazol-1-yl)-3-propyl]guanidine;  
or a pharmaceutically acceptable salt of any of said compounds.

12. A compound of the following Formula:



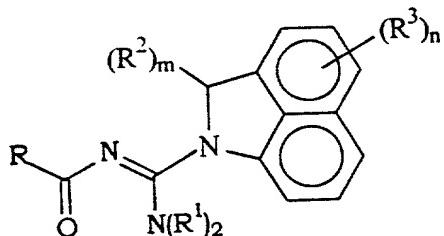
wherein R is an optionally substituted cyclic alkyl; optionally substituted carbocyclic aryl; optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; optionally substituted aralkyl; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl;

each R<sup>1</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted or unsubstituted carbocyclic aryl; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and 1 to about 3 hetero atoms;

each R<sup>2</sup> and each R<sup>3</sup> are each independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted aminoalkyl, optionally substituted carbocyclic aryl, or optionally substituted aralkyl;

m is an integer of from 0-6; and n is an integer of from 0-4; and pharmaceutically acceptable salts thereof.

13. A compound of the following Formula:



wherein R is an optionally substituted cyclic alkyl; optionally substituted carbocyclic aryl; optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; optionally substituted aralkyl; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl;

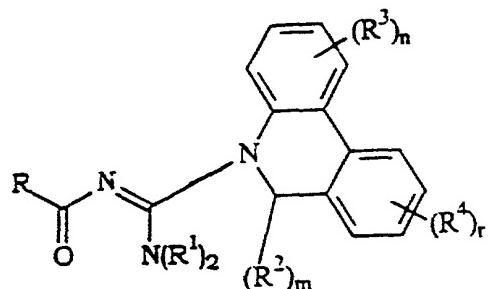
each R¹ is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted or unsubstituted carbocyclic aryl; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and 1 to about 3 hetero atoms;

each R<sup>2</sup> and each R<sup>3</sup> are each independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally

substituted alkylsulfonyl, optionally substituted aminoalkyl, optionally substituted carbocyclic aryl, or optionally substituted aralkyl;

m is 0, 1 or 2; and n is 0, 1, 2, 3, 4, 5 or 6; and pharmaceutically acceptable salts thereof.

14. A compound of the following Formula:



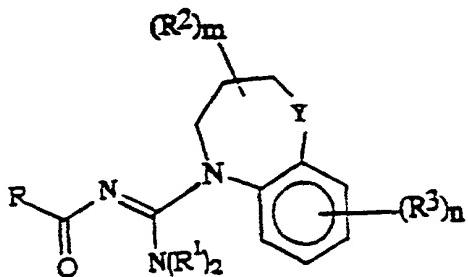
wherein R is an optionally substituted cyclic alkyl; optionally substituted carbocyclic aryl; optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; optionally substituted aralkyl; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl;

each R<sup>1</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted or unsubstituted carbocyclic aryl; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and 1 to about 3 hetero atoms;

each R<sup>2</sup>, each R<sup>3</sup> and each R<sup>4</sup> are each independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted aminoalkyl, optionally substituted carbocyclic aryl, or optionally substituted aralkyl;

m is 0, 1 or 2; and n and r are each independently 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

15. A compound of the following Formula:



wherein R is an optionally substituted cyclic alkyl; optionally substituted carbocyclic aryl; optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; optionally substituted aralkyl; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl;

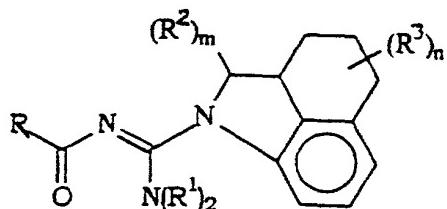
each  $R^1$  is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted or unsubstituted carbocyclic aryl; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and 1 to about 3 hetero atoms;

each  $R^2$  and each  $R^3$  are each independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted aminoalkyl, optionally substituted carbocyclic aryl, or optionally substituted aralkyl;

Y is optionally substituted methylene, -O-, -S-, -S(O)-, -S(O<sub>2</sub>)-, or optionally substituted -N-,

m is an integer of from 0-6; and n is 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts of those compounds.

16. A compound of the following Formula:



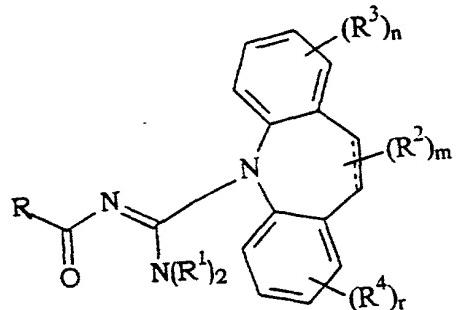
wherein R is an optionally substituted cyclic alkyl; optionally substituted carbocyclic aryl; optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; optionally substituted aralkyl; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl;

each  $R^1$  is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted or unsubstituted carbocyclic aryl; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and 1 to about 3 hetero atoms;

each  $R^2$  and each  $R^3$  are independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted aminoalkyl, optionally substituted carbocyclic aryl, or optionally substituted aralkyl;

m is 0, 1 or 2; and n is an integer equal to 0-9; and pharmaceutically acceptable salts thereof.

17. A compound of the following Formula:



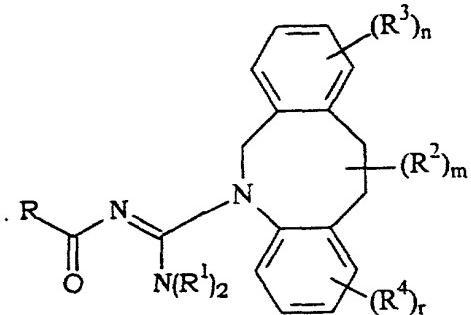
wherein R is an optionally substituted cyclic alkyl; optionally substituted carbocyclic aryl; optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; optionally substituted aralkyl; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl;

each R<sup>1</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted or unsubstituted carbocyclic aryl; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and 1 to about 3 hetero atoms;

each R<sup>2</sup>, each R<sup>3</sup> and each R<sup>4</sup> are each independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted aminoalkyl, optionally substituted carbocyclic aryl, or optionally substituted aralkyl;

m is 0, 1, 2, 3 or 4; and n and r are each independently 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

18. A compound of the following Formula:



wherein R is an optionally substituted cyclic alkyl; optionally substituted carbocyclic aryl; optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms; optionally substituted aralkyl; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl;

each R<sup>1</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted or unsubstituted carbocyclic aryl; or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and 1 to about 3 hetero atoms;

each R<sup>2</sup>, each R<sup>3</sup> and each R<sup>4</sup> are each independently hydrogen, halogen, hydroxyl, azido, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted aminoalkyl, optionally substituted carbocyclic aryl, or optionally substituted aralkyl;

m is an integer of from 0-6; and n and r are each independently 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

19. A compound of any one of claims 1-9 or 10-18 wherein R is an optionally substituted cyclic alkyl; optionally substituted carbocyclic aryl; optionally substituted alkylaryl; an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to about 8 ring members in each ring and from 1 to about 3 hetero atoms

20. A compound of any one of claims 1-9 or 10-18 wherein R is optionally substituted cyclic alkyl.

21. A compound of any one of claims 1-9 or 10-18 wherein R is optionally substituted carbocyclic aryl.

22. A compound of any one of claims 1-9 or 10-18 wherein R is optionally substituted phenyl or naphthyl.

23. A compound of any one of claims 1-9 or 10-18 wherein R is optionally substituted heteroaromatic or heteroalicyclic.

24. A compound of any one of claims 1-9 or 10-18 wherein R is optionally substituted carbocyclic aralkyl.

25. A compound of claim 9 or 15 wherein Y is optionally substituted methylene.

26. A compound of any one of claims 1-9 or 12-25 wherein at least one R<sup>1</sup> group is hydrogen.

27. A compound of any one of claims 1-9 or 12-25 wherein both R<sup>1</sup> groups are hydrogen.

28. A compound of any one of claims 1-9 or 12-25 wherein at least one R<sup>1</sup> group is optionally substituted alkyl.

29. A compound of any one of claims 1-9 or 12-25 wherein at least one R<sup>1</sup> group is alkyl having 1 to 3 carbon atoms.

30. A compound of any one of claims 1-9 or 12-25 wherein both R<sup>1</sup> groups are optionally substituted alkyl.

31. A method of treating a nerve degeneration disease comprising administering to a mammal suffering from or susceptible to said disease a therapeutically effective amount of a compound of any of claims 1-30.

32. A method of treating a neurodegenerative disease comprising administering to a mammal suffering from or susceptible to said disease a therapeutically effective amount of a compound of any of claims 1-30.

33. A method of treating Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Down's Syndrome or Korsakoff's disease, Cerebral Palsy, or epilepsy, comprising administering to a mammal suffering from or susceptible to said disease a therapeutically effective amount of a compound of any of claims 1-30.

34. A method of treating or preventing nerve cell death or degeneration comprising administering to a mammal suffering from or susceptible to nerve cell death or degeneration a therapeutically effective amount of a compound of any one of claims 1-30.

35. The method of claim 34 wherein the nerve cell death or degeneration is associated with hypoxia, hypoglycemia, brain or spinal cord ischemia, retinal ischemia or brain or spinal cord trauma.

36. A method of treating a mammal suffering from or susceptible to stroke or heart attack comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-30.

37. A method of treating a mammal suffering from or susceptible to brain or spinal cord trauma comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-30.

38. A method of treating a mammal suffering from or susceptible to pain including chronic pain or neuropathic pain, peripheral necropathy, migraines, shingles, emesis, narcotic withdrawal symptoms or age-dependent dementia, comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-30.

39. A method of treating a mammal suffering from or susceptible decreased blood flow or nutrient supply to retinal tissue or optic nerve, or retinal ischemia or trauma, or optic nerve injury, or glaucoma, comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-30.

40. A method of treating a mammal suffering from or susceptible to post-surgical neurological deficits or neurological deficits associated with cardiac arrest, comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-30.

41. A method for treating an infection in a mammal, comprising administering to a mammal suffering from or susceptible to an infection an effective amount of an aminoglycoside antibiotic and a compound of any one of claims 1-30.

42. The method of claim 41 wherein the mammal is suffering from an infection of a Gram negative bacteria or a Gram positive bacteria.

43. A method of any one of claims 31-42 wherein the mammal is a human.

44. A pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of any one of claims 1-30 and a pharmaceutically acceptable carrier.

45. A compound of any one of claims 1-30 that is radiolabelled.

ABSTRACT OF THE DISCLOSURE

The present invention relates to pharmaceutically acceptable compounds, including acylguanidine compounds, and methods of treatment and pharmaceutical compositions that utilize or comprise one or more such compounds. Compounds of the invention are particularly useful for the treatment or prophylaxis of neurological injury and neurodegenerative disorders.